THE REGIOSPECIFIC SYNTHESIS OF N-OXIDIZED AND N-QUATERNIZED POLYCYCLIC POLYAZINES AND SYNTHESIS OF UNSYMMETRICAL QUATERPYRIDINES USING PALLADIUM-CATALYZED CROSS-COUPLING

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
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This work is dedicated to my parents, Michael and Patricia Cruskie, whom I respect, admire and love dearly.

This dedication also extends to my sister, brother, grandparents, aunts, uncles, cousins, godchildren and dog.

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Finally, the author would like to acknowledge Maggie Mae for keeping him sane during the course of this work.

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THE REGIOSPECIFIC SYNTHESIS OF N-OXIDIZED AND N-QUATERNIZED POLYCYCLIC POLYAZINES AND THE SYNTHESIS OF UNSYMMETRICAL QUATERPYRIDINES USING PALLADIUM-CATALYZED CROSS-COUPLING

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Chairperson: John A. Zoltewicz
Major Department: Chemistry

Palladium-catalyzed cross-coupling reactions between a hetarylborane or stannane and N-oxidized or N-quaternized hetaryl halides provide polyazines of unequivocal structure in terms of the location of the N-functionalized group. Examples of several ring systems are given to illustrate the scope and limitations of the new synthetic method.

N-Oxides of tributylstannylated pyridine, quinoline and isoquinoline and N-methylated tributylstannylpyridine and quinoline were readily prepared, many for the first time. In the presence of a Pd catalyst these materials cross-couple with various chloro, bromo and iodo hetaryl halides to give polycylic polyazines having the N-functional group placed unequivocally in eleven different polycyclic ring systems.

The use of a tosylate as a counterion with quaternized salts minimized decomposition of the stannane.

5-Carbamoyl-2,3′-bipyridine model compound was N-methylated and N-oxidized at the less reactive 2-pyridyl ring for the first time. Two different schemes were developed.

The quaterpyridine called nemertelline was synthesized for the first time. The proton NMR spectrum of 3,2′:3′:2′′:4′′:3′′-quaterpyridine shows that it is not the natural product isolated from the hoplonemertine sea worm. The correct structure of the natural product has been identified as 3,2′:3′,4′′:2′′,3′′′-quaterpyridine. It was synthesized using a key palladium-catalyzed cross-coupling step and X-ray analysis confirmed the structure as well as providing its conformation in the solid state.

2,2′-Bipyridine in the presence of LDA gives 2,2′:3′,2′′:6′′,2′′′-quaterpyridine resulting from a reaction at the 3 position of one bipyridine and the 6 position of another, not 2,2′:4′,2′′:6′′,2′′′-quaterpyridine coming from the reaction at the 4 and 6 position as originally claimed by others. An independent synthesis of 2,2′:4′,2′′:6′′,2′′′-quaterpyridine involved palladium-catalyzed cross-coupling of 2′,6-dichloro-2,4-bipyridine and 2-(tributylstannyl)pyridine. The correct structure follows from analysis of the COSY, NOE difference and proton NMR spectra.

Model unsymmetrical quaterpyridines were prepared by palladium-catalyzed cross-coupling of a pyridyl borane or

stannane to a chlorinated bipyridine. A pyridyl N-oxide synthon was used to regioselectively introduce the required α-chloro group.

CHAPTER 1
INTRODUCTION

Palladium is an extremely useful reagent in that it catalyzes a wide variety of known organic reactions. Palladium salts and complexes have been widely used in many organic reactions such as double bond isomerizations, molecular rearrangements, oxidations, allylic substitutions and eliminations, dimerizations and oligomerizations, carbonylations, cyclopropanations, reductions, and couplings.[1] Since there are few basic reactions that generate a new carbon-carbon bond, palladium-assisted coupling reactions have become an important tool for organic chemists.

Palladium-assisted coupling reactions proceed by several closely related pathways. In all of these pathways, the initial step is believed to be the formation of an organopalladium salt. There are four general ways in which these organopalladium salts can be formed. These are (i) the direct metallation of a hydrocarbon, arene, or a heterocylic compound with a Pd(II) salt; (ii) the addition of a palladium(II) salt to an acetylene, diene, or alkene; (iii) the use of an organic group from an organometallic reagent such as a mercurial, stannane, borane, lithium, zinc, or

Grignard reagent in an anion exchange on palladium(II); and (iv) the oxidative addition of an organic halide, triflate, acetate, or ether onto a palladium(0) moiety.[1]

The formation of the organopalladium complex now allows the possibility of manufacturing coupling products by one of three plausible routes: (i) disproportionation to form a diorganopalladium intermediate which can reductively eliminate to give a homocoupled product; (ii) addition of the oxidative addition complex to an alkene, diene, or acetylene followed by reductive elimination or the elimination of palladium halide or hydride to produce the coupled products; or (iii) formation of a diorganopalladium species by transmetalation of another organometallic reagent, which can again reductively eliminate to produce a cross-coupled product.[1]

In palladium-catalyzed cross-couplings, and more specifically the Stille[2] and Suzuki[3] coupling reactions, the catalytic process consists of an oxidative addition, transmetalation, and reductive elimination (Figure 1-1). The Stille coupling reaction utilizes a palladium catalyst and is defined as the cross-coupling between organic electrophiles (typically an organic halide or triflate) and organostannanes (Figure 1-2).[2] The organic halide or triflate participates in the oxidative addition and the organostannane takes part in the transmetalation. The Suzuki coupling reaction utilizes an organoborane or boronic acid instead of an organostannane in the transmetalation. The increased availability and general

stability of organostannanes and boranes, the usually mild reaction conditions, and the compatability of this chemistry with virtually any functional group, have made the Stille and Suzuki couplings quite popular among synthetic chemists. In fact, a survey of applications of transition metal-mediated cross-coupling reactions for the year 1992 shows that the Stille and Suzuki reactions account for over 75% of all cross-couplings.[4]

Figure 1-1

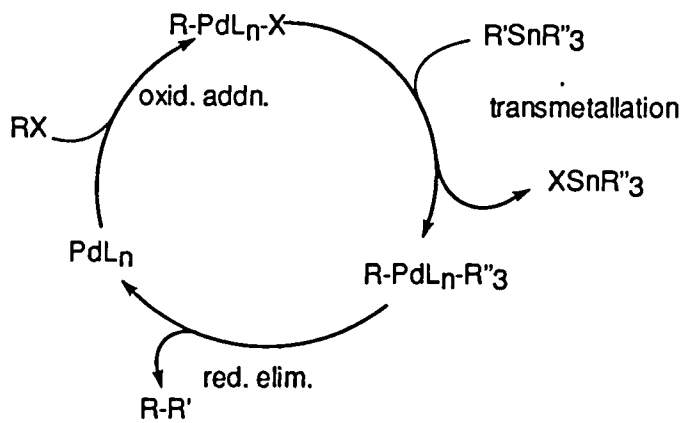
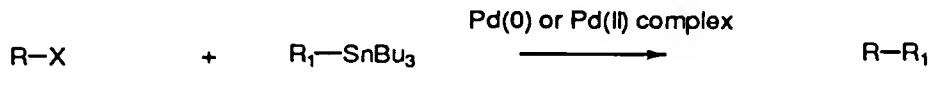


Figure 1-2 - Generalized Stille coupling reaction



R and R_1 = alkene, alkyne, aryl, hetaryl

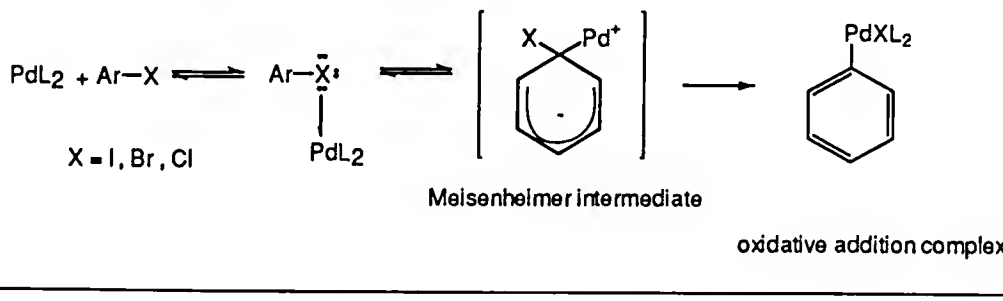
X= I, Br, Cl, OTf

Several fundamental questions arise when considering the transformations which occur during any organic reaction: What is the rate determining step? What is the exact mechanism of this step? Is it possible to facilitate this step? What are the side reactions involved with this process? Is it possible to suppress such side reactions? These types of questions have led to a substantial amount of research toward fully understanding the scope and limitations of the three-step process in palladium-catalyzed cross-couplings. During the catalytic process, considerable electronic demands are made on the palladium catalyst. Oxidative addition requires an electron rich metal so that oxidation will be favored[5,6], but transmetalation requires an electron deficient palladium for the nucleophile to attack the metal center.[7] Depending on the reagents and conditions used, the exact mechanism may vary and either oxidative addition or transmetalation can be rate determining. To better understand the catalytic process, each step must be considered individually.

It has become generally accepted that oxidative addition of organic halides or triflates to Pd(0) complexes proceeds through an unsaturated 14-electron Pd(0) intermediate.[8-10] Ligand dissociation leads to open coordination sites on palladium which can now allow the halide or triflate to initially coordinate to the Pd(0) intermediate. After initial coordination, the oxidative addition product could essentially come from nucleophilic aromatic substitution with a

Meisenheimer intermediate (Figure 1-3).[9-11] The Meisenheimer intermediate is influenced by C-halogen bond strength, while the transition state preceding the intermediate is mainly influenced by the electrophilicity of the carbon atom being attacked.[9] The relative rate at which organic halides or triflates oxidatively add to palladium is generally on the order of I > Br > Cl > OTf, suggesting that the transition state succeeding the Meisenheimer intermediate is rate determining in oxidative addition.[12]

Figure 1-3

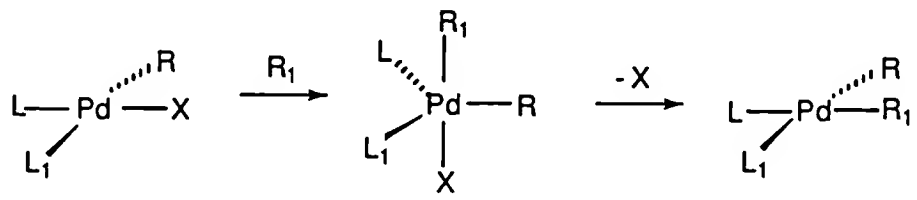


Depending on the type of ligands used with the catalyst, the irreversible formation of the oxidative addition complex can very often lead to a stable material.[13-15] Recent studies have suggested that the type of ligands used with palladium can play a very important role in the catalytic process.[4,7] Among such developments is the discovery of a large ligand effect in Stille reactions which can produce rate enhancements of $>10^3$ over original conditions.[7] The "ligand effect" occurs when softer ligands are used to coordinate to palladium such

as triphenylarsine or tri(2-furyl)phosphine instead of the typical triphenylphosphine. Triphenylarsine and tri(2-furyl)phosphine do not coordinate to palladium as strongly as triphenylphosphine which allows for ligand dissociation more readily. Ligand dissociation can lead to faster formation of the oxidative addition complex as well as open coordination sites on the oxidative addition complex for transmetalation.

While the mechanism for oxidative addition is reasonably well understood,[16] some evidence suggests that transmetalation is rate determining in most cross-couplings.[17,18] Unfortunately, little is known about the mechanism of this step although some indirect information has come from studies on transmetalation at platinum(II).[19-24] The Stille and Suzuki coupling reactions use different reagents in the transmetalation and therefore, will be addressed separately.

Figure 1-4



In the Stille coupling, transmetalation consists of a substitution process at a square-planar Pd(II) complex, where

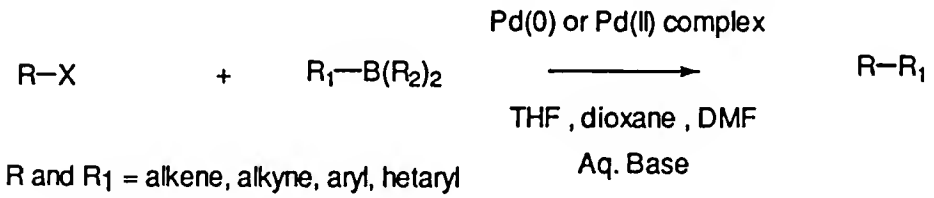
the nucleophile is the organostannane and the leaving group is the halide or triflate. Therefore, the reaction might be expected to proceed through a classical associative process[25] in which the nucleophile approaches the plane of the complex perpendicularly. As a result, an unstable pentacoordinated intermediate is formed which then releases the leaving group (Figure 1-4).[7]

Recently, work by Farina *et al* has shown that with olefinic stannanes, ligand dissociation and formation of a palladium-stannane π-complex are the key steps in transmetalation.[7]

An important development in facilitating transmetalation in Stille coupling reactions involves the use of cocatalytic copper iodide, along with palladium.[26-29] Farina *et al* have shown that with triphenylphosphine and palladium(0), cocatalytic copper iodide can give a >100-fold rate increase over a typical Stille reaction.[28] Though there is widespread use of copper iodide in coupling reactions, its extact functions in the reaction are not completely understood. One plausible role is that the copper is involved in stannyl/copper transmetalation,[27] thus producing an organocopper moiety which could then transmetalate onto the oxidative addition complex more readily than the stannane itself. Another effect of copper iodide is that it acts as a scavenger for free ligands thereby leaving coordination sites on the oxidative addition complex for transmetalation.

When using an arylstannane, one of the major side reactions is homocoupling of the arylstannane to give a biaryl. Mechanistically, the reaction may be initiated by oxidative addition of palladium into the carbon-stannyl bond of the arylstannane. Oxidation of the aryl-palladium-stannyl species involves O_2 and seems to have a radical component; this presumably complex step may be followed by transmetalation with a second arylstannane and then reductive elimination to give the biaryl.[4] In certain cases, removing O_2 with many freeze-thaw cycles under vacuum has suppressed homocoupling to some degree.[4,30]

Figure 1-5 - Generalized Suzuki coupling reaction



R and R_1 = alkene, alkyne, aryl, hetaryl

X = I, Br, Cl

R_2 = Et , OH , BBN

The Suzuki coupling uses an organoborane or boronic acid instead of an organostannane in transmetalation. The reaction is usually done under aqueous alkaline conditions along with a palladium reagent (Figure 1-5). The use of an alkaline medium for such coupling reactions seems to be a necessary

requirement in order to give an intermediate "ate" complex of the boron reagent on addition of hydroxide ion.[3,31] It is this "ate" complex that tranfers an organic ligand to the oxidative addition complex in the transmetallation.[1,3,13,32,33] Though the aqueous alkaline conditions have become a somewhat standard procedure in this type of reaction, there are examples of coupling reactions with organoboranes or boronic acids under alternate conditions.[31,34,35]

A classical problem in heterocyclic chemistry deals with the question of how to control and thereby direct N-oxidation or N-quaternization to a single, selected annular nitrogen atom of a polycyclic polyazine. One solution to this problem is to preform the polycyclic polyazine with the use of palladium-catalyzed cross-coupling and then selectively functionalize the desired annular nitrogen atom. Depending on the reactivity of the nitrogen atom, it may be functionalized directly or by a protection/functionalization/deprotection pathway. The protection/functionalization/deprotection pathway will be discussed further in chapter 4.

A potential way to eliminate the protection/deprotection steps would be to functionalize the desired nitrogen atom prior to linking the rings together. Using palladium-catalyzed cross-coupling chemistry, either the hetaryl halide or the organometallic reagent could be N-oxidized or N-quaternized. Cross-coupling now leads to the N-functionalized polycyclic polyazine where it is unequivocally known which

nitrogen atom is N-functionlized. The scope and limitations of these processes will discussed in chapters 2 and 3.

The development of palladium-catalyzed cross-coupling reactions has exploded in recent years and now allows for easy construction of polyhetarenes that would otherwise be difficult to construct. For example, there are 426 theoretically possible quaterpyridines, both symmetrical and unsymmetrical, with only seven of these being reported in the literature. Five are symmetrical structures of the type A-B-B-A; they are easily prepared by homocoupling the A-B portions under a variety of conditions.[36-40] Both of the two reported unsymmetrical quaterpyridines were originally assigned incorrectly. They include the natural product nemertelline, which was first isolated in 1976 from the phylum of the marine worms called nemertines,[41] and the product from the reaction of LDA with 2,2′-bipyridine.[42] Both structures have been corrected by an independent synthesis involving strategies developed in this document; they are based on palladium(0)-catalyzed cross-coupling chemistry.

CHAPTER 2
DIRECT PREPARATION OF N-QUATERNIZED AND N-OXIDIZED POLYCYCLIC POLYAZINES BY PALLADIUM-CATALYZED CROSS-COUPLING--AN UNEQUIVOCAL ISOMER SYNTHESIS

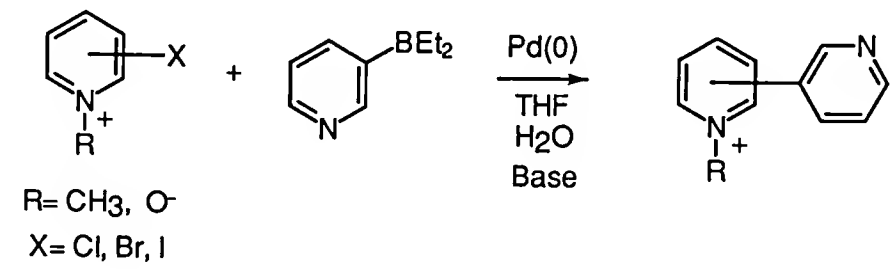
Introduction

The number of recently reported transition metal-catalyzed cross-coupling reactions used to prepare polyaryl and polyhetaryl compounds has grown explosively, palladium being the metal of choice.[3,43-46] But the number of preparations of N-oxides by this means using preformed N-oxides in the coupling reaction has been very limited.[47-50] For example, the ability of a 2-bromopyridine N-oxide to undergo coupling without competing nucleophilic substitution to replace the bromine atom has been demonstrated[47] and control over the location of the N-oxide group within a pyrazine ring by using a preformed chloropyrazine-N-oxide in a cross-coupling reaction has been reported.[48-50] The preparation of N-quaternized polyhetaryls by such coupling reactions using quaternized starting materials seems not to have been exploited at all.

We will employ two types of coupling reactions in the preparation of N-oxidized or N-quaternized polycyclic polyazines. One method effects coupling under aqueous alkaline conditions with diethyl(3-pyridyl)borane and an N-oxidized or

N-quaternized hetaryl halide along with a palladium reagent, now something of a standard procedure known as the Suzuki reaction (Figure 2-1).[3,44,51]

Figure 2-1 - General Suzuki-type reaction

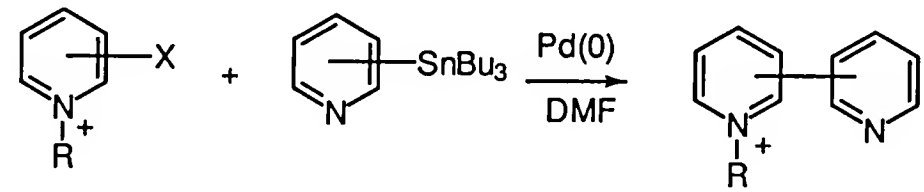


R= CH_3, O^-
X= Cl, Br, I

The use of an alkaline medium for such coupling reactions seems to be a necessary requirement in order to give an intermediate "ate" complex of the boron reagent on addition of hydroxide ion.[31] This "ate" complex then transfers its aromatic ligand to the palladium oxidative addition product of the halide prior to product formation in a final reductive elimination step.[1,13,32,33] Pyridylboronic acids have been made to cross-couple in a nonaqueous solvent such as DMF containing triethylamine in the presence of a palladium catalyst.[34] Boranes couple with triflates in a suspension of Na_3PO_4 in dry dioxane containing a palladium catalyst.[31] Oxidative addition complexes of palladium and halogenated heterocycles have been isolated and characterized.[13-15]

Both N-oxidation and especially N-quaternization are known to activate enormously a halogenated hetarene for nucleophilic substitution on displacing the halogen atom[52,53] and this knowledge may have prevented others from attempting the coupling reactions we now report. For example, methoxydechlorination of 2-chloro- and 4-chloropyridine N-oxides is some 10^{12} times faster than that of chlorobenzene and the same reaction for 2-chloro- and 4-chloro-1-methylpyridinium ion is about 10^{21} and 10^{19} times faster, respectively, than substitution of chlorobenzene.[52,53] Moreover, under alkaline condition, N-quaternized hetarenes may degrade by ring cleavage reactions.[54] While nucleophilic substitution by the S_NAr mechanism is largely insensitive to the identity of the halogen nucleofuge,[52] cross-coupling rates decrease in the order I > Br > Cl. Clearly then, the choice of a halogen atom and the reaction conditions, especially pH, is expected to be quite important for the success of the cross-coupling reaction of hydrolytically labile substrates.

Figure 2-2 - General Stille-type reaction



R= CH_3, O^-

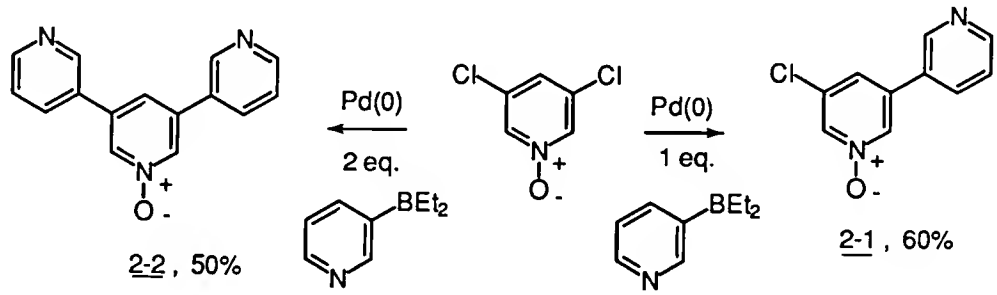
X= Cl, Br, I

In certain cases, the coupling of N-functionalized halo-heteroaromatic compounds and stannylhetarenes under non-aqueous conditions was examined. Known as the Stille coupling reaction, it utilizes a stannane instead of a borane and occurs under non-aqueous conditions such as dry THF, dioxane, or DMF (Figure 2-2).

Results and Discussion

The compounds we selected to be prepared were designed to illustrate the power of our approach and to establish some of its scope and limitations. Consider our synthesis of 5-chloro-3,3′-bipyridine-1-oxide (2-1) from 3,5-dichlorpyridine-1-oxide[55] and diethyl-3-pyridylborane (Figure 2-3). The position of the oxide ligand with respect to the chlorine atom is unequivocal because the N-oxide group was present on the chlorinated ring at the start. By contrast, attempts to N-oxidize 5-chloro-3,3′-bipyridine following a similar coupling reaction to prepare the unoxidized material would not be expected to provide the 1-oxide as the major product. Mixed mono N-oxides are likely because the electron-withdrawing chlorine atom would have caused N-oxidation to take place at the more reactive unsubstituted ring to give the isomeric 1′-oxide as the major product and 2-1 as the minor product. The N-oxidation of 3,3′-bipyridine itself is known to give a mixture of mono- and di-N-oxides that are hard to separate.[56]

Figure 2-3

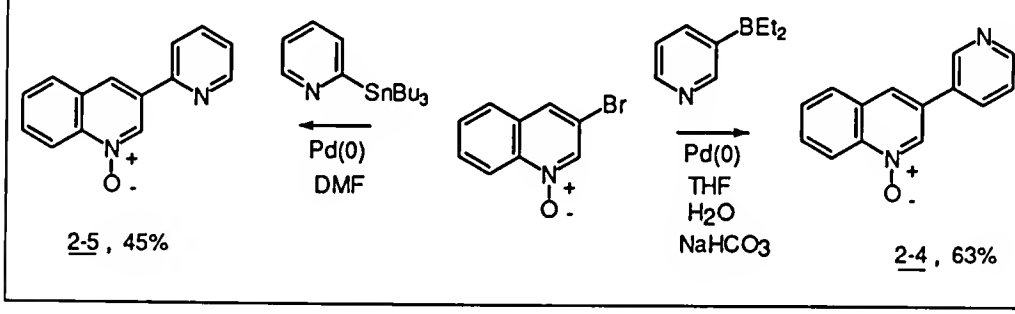


The direct preparation of the symmetrical 3,3′:5′3′′-terpyridine (2-2) having the center ring N-oxidized as in 2-2 by direct N-oxidation is an even greater challenge because all three pyridyl rings are expected to have similar reactivities. Our synthesis of 2-2 is both trivial and unequivocal in that the same 3,5-dichloropyridine-1-oxide[55] used to prepare 2-1 was employed to synthesize 2-2 but now two equivalents of diethyl(3-pyridyl)borane were present along with a carbonate buffer (Figure 2-3). Surprisingly, the nonoxidized form of 2-2 was prepared from 3,5-dibromopyridine in 1936 by a palladium on $CaCO_3$ coupling reaction under heterogeneous conditions[57] that substantially predates its recent synthesis using the complexed palladium metal.[58]

3-(3-Pyridyl)quinoline 1-oxide (2-4) was easily synthesized from diethyl(3-pyridyl)borane and 3-bromoquinoline 1-oxide[59] (2-3) in the presence of a bicarbonate buffer, Scheme

4. Here the N-oxide unit is located on a nitrogen atom highly sterically hindered by the peri position[60] and so 2-3 would have been formed only as a minor product on N-oxidation of the preformed pyridylquinoline. To further extend this approach, it was shown that Stille-type conditions will afford coupled products as well. In dry DMF, 2-3 coupled to 2-(tributylstannyl)pyridine to give 3-(2-pyridyl)quinoline-1-oxide (2-5) in 45% yield (Figure 2-4).

Figure 2-4



A substrate even more activated for nucleophilic substitution and ring cleavage by hydroxide ion is found in 3-iodo-1-methylpyridinium ion.[61] 1-Methyl-3,3′-bipyridinium ion[1] was formed from the 3-iodopyridine and diethyl(3-pyridyl)borane. While in alternate syntheses the quaternizations of 3,3′-bipyridine to yield 1-methyl-3,3′-bipyridinium ion is a simple and unequivocal reaction, our coupling method illustrates the important principle that even

[1] This compound was originally synthesized by C.D. Dill.

quaternized substrates very highly activated for nucleophilic substitution and ring cleavage may be employed in the cross-coupling under aqueous alkaline conditions. This approach would be useful, for example, to prepare unsymmetrically carbon substituted derivatives of 1-methyl-3,3′-bipyridinium ion of known and controlled structure as in the case of 2-1.

The failure of 4-chloro-1-methylpyridinium iodide to couple with diethyl(3-pyridyl)borane even under weakly basic conditions promted us to try Stille-type conditions. The move to 3-(tributylstannyl)pyridine and dry DMF allowed the formation of the coupled product, 1-methyl-3′,4-bipyridinium iodide (2-9), in a 20% yield. Due to the similar reactivity between the two annular nitrogens, selective quaternization of preformed 3,4-bipyridine, undoubtably, would have resulted in a mixture.

The reactivity of halogenated N-methylquinolinium and N-methylisoquinolium salts also were examined. These bicyclic materials are still more activated than the pyridinium ions for nucleophilic substitution[62] and for pseudo-base formation by the addition of hydroxide ion, often accompanied by ring cleavage.[54,63] Several attempts were necessary to find the proper alkaline buffer to minimize side-reactions. Borate, phosphate and bicarbonate buffers were examined in order to lower successively the reaction pH.

3-Pyridylated quinolinium ion 2-7 was recovered as product in moderate yield when bicarbonate was used to buffer

the reaction mixture consisting of diethyl(3-pyridyl)borane and 3-bromo-1-methylquinolinium ion[64] and the palladium catalyst. This is a useful preparation because quaternization of preformed 3-(3-pyridyl)quinoline is not expected to yield 2-7 directly, owing to considerable steric hindrance by the peri position.[60] Replacing the aqueous solvent by anhydrous DMF did not lead to an increase in the yield of product. Bicarbonate has been used in palladium induced coupling reactions of thiopheneboronic[51] and pyridylboronic acids,[65] for example.

Employing 4-bromo-2-methylisoquinolinium ion[66] and benzeneboronic acid it was possible to prepare the 4-phenylated isoquinolinium ion with borate base. Unfortunately, attempts to make the 4-pyridylated isoquinolinium ion (2-8) using borate, phosphate or bicarbonate buffers were unsuccessful due to degradation of the heterocyclic cation when the reaction was run with two phases, the alkaline layer containing the isoquinolinium ion. However, the addition of some methanol to make the mixture homogeneous allowed 2-8 to be isolated in 43% yield in the presence of a borate buffer.[2] A slight improvement in the yield of 2-8 (51%) was seen when 4-bromo-2-methylisoquinolinium iodide was coupled with 3-(tributylstannyl)pyridine using a palladium(0) catalyst in dry DMF, Figure 2-5 (Stille-type conditions). The unquaternized precursor of 2-8 has been made by a palladium coupling route.[67]

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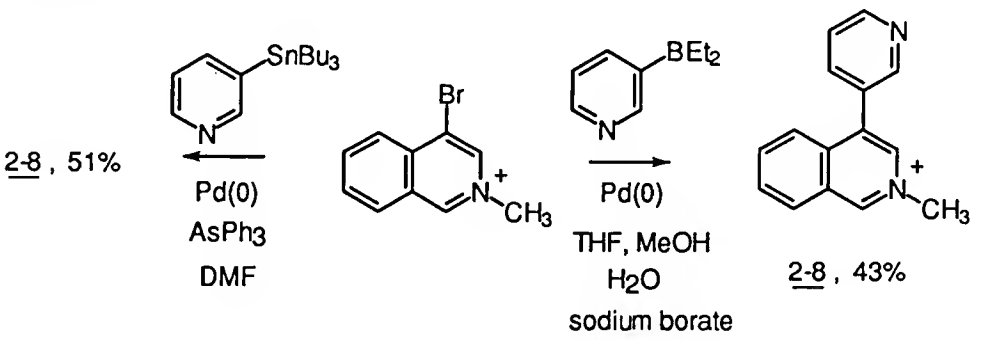
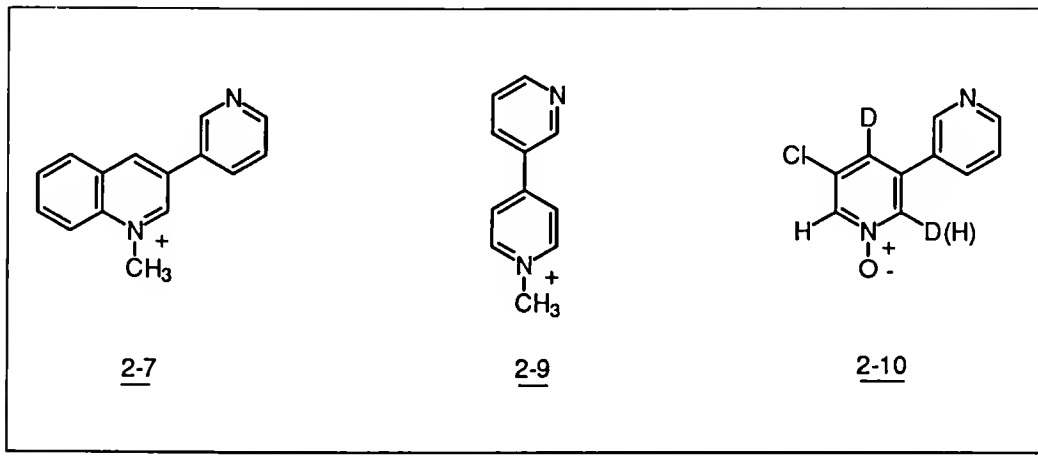
[2] Work was kindly done by Carlton D. Dill

Figure 2-5



Having demonstrated that weakly basic buffers are sufficient to induce cross-coupling, a perdeuterated substrate was examined in order to learn whether it is possible to employ an isotopically labelled reagent in the coupling process. The deuterium isotopes at the equivalent 2,6 positions in 3,5-dichloropyridine-1-oxide-2,4,6-d_3 are known to be removed easily with dilute alkali[68] and their presence therefore serves as a sensitive test of reaction conditions. Partially deuteriated product 2-10 was prepared in the presence of bicarbonate from the essentially completely labelled (95%) dichloride.[55] No deuterium was found at position 6, 65% D at position 2 and the original amount at 4. Unequal labelling of the 2 and 6 positions of 2-10 indicates that some of the hydrogen isotope was removed both during and following the formation of coupling product, the former site being more activated for isotope exchange than the latter in the product.

The coupling conditions are mild enough to allow selected sites to retain their hydrogen label.



2-7 2-9 2-10

Conclusions

Palladium-catalyzed cross-coupling may be used successfully to prepare N-oxidized and N-quaternized polycyclic polyazines of unequivocal structure under aqueous conditions (Suzuki-type conditions). An isotopically labelled substrate may be employed as a reactant when the buffer is selected judiciously so that a hydrogen isotope at carbon will be retained. It seems likely that other types of N-functionalized compounds such as N-amines can be prepared by our method.

It is also possible to prepare N-functionalized polcyclic polyazines with palladium-catalyzed cross-coupling under non-aqueous conditions (Stille-type conditions). A slighly better yield was obtained in the synthesis of 2-8 under Stille-type

conditions with 3-(tributylstannyl)pyridine. While Suzuki-type conditions did not yield any coupled product with 4-chloro-1-methylpyridinium iodide and diethyl(3-pyridyl)borane, some product was obtained with Stille-type conditions. However, Suzuki-type conditions gave a better yield over Stille-type conditions in the coupling of 3-bromoquinoline-N-oxide.

The synthesis of isomers having a bond to the 2 and 4 position of N-quaternized materials is still more challenging due to the enhanced ease of nucleophilic substitution of the halogenated precursors.

CHAPTER 3
A GENERAL METHOD OF SYNTHESIS FOR REGIOSPECIFICALLY N-OXIDIZED OR N-QUATERNIZED POLYCYCLIC POLYAZINES BY PALLADIUM-CATALYZED CROSS-COUPLING OF N-OXIDIZED OR N-QUATERNIZED HETARYL STANNANES

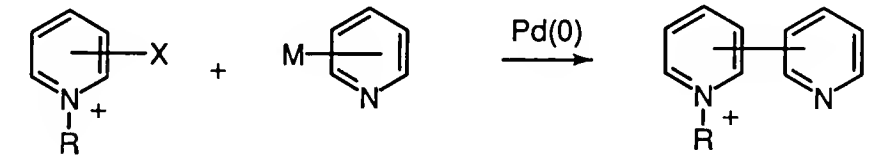
Introduction

A classical problem in heterocyclic chemistry deals with the question of how to control and thereby direct N-oxidation or N-quaternization to a single, selected annular nitrogen atom of a polyazine or polycyclic polyazine.

We have devised a simple and direct solution to this old challenge. We use the recently developed and now highly popular palladium-catalyzed cross-coupling reaction of a hetaryl halide and a hetaryl organometallic compound to synthesize a polyazine. But unlike the approaches of others, we N-oxidize or N-quaternize the desired annular nitrogen atom *prior* to linking the rings together. Thus, the regiochemistry of the final product is assured and unequivocal.

In our original application of this approach,[69] the hetaryl halide was functionalized either by N-oxidation or N-methylation and then coupled to a hetarylborane (in a Suzuki-type reaction) or a hetarylstannane (in a Stille-type reaction), Figure 3-1.[3,70] Although this method is both attractive and useful it does have some limitations.

Figure 3-1



R= CH_3, O^- M= BEt_2, $SnBu_3$

X= Cl, Br, I

The Suzuki-type reaction generally requires aqueous alkali to generate the reactive hydroxide ion adduct of the borane or boronic acid, an "ate" complex.[3,30,70,71] Under aqueous conditions, the N-oxidized or N-quaternized hetaryl halide is highly activated for nucleophilic substitution, hydroxydehalogenation,[52,72] as well as other undesirable side-reactions such as hydrolytic ring cleavage.[54] However, nonaqueous conditions[31,34] and more recently fluoride ion under aqueous and nonaqueous conditions[35] also have been found to be useful. Boronic acid esters may be made to cross-couple under nonaqueous conditions in the presence of both palladium and thallium(I) catalysts.[73]

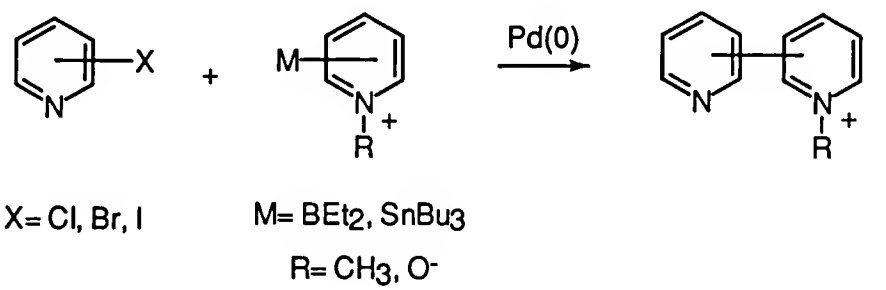
One way to overcome this problem would be to use a hetarylstannane and non-aqueous conditions such as dried DMF. As seen in chapter 2, Stille-type conditions did slightly improve yields in the coupling of N-quaternized hetaryl

halides but not with N-oxidized hetaryl halides. Others have taken this approach and coupled a stannane with a halogenated N-oxide.[49,50]

Another approach might make use of a hetaryl halide that is not N-oxidized or N-quaternized and thereby minimize the possibility of side reactions. In the Suzuki-type reaction, the hetaryl borane or boronic acid now would be functionalized at the annular nitrogen atom. Unfortunately, the necessary N-functionalized hetaryl boranes and boronic acids are largely unknown materials, with good reason. For example, the N-methylation of a 3-pyridyl borane has not been achieved in spite of repeated attempts[44,74,75] because this borane exists in solution as a cyclic tetramer in which the nitrogen atom of one molecule is coordinated to the boron atom of a second.[76] Thus, the lone electron pair on the nitrogen atom is unavailable for nucleophilic reaction. N-methylation of a 3-pyridyl borane was achieved only when the borane first was converted to an "ate" complex with cyanide ion to destroy the oligomer. Unfortunately, the cyanide is retained in the betaine final product.[44] Other hetaryl boranes are known to have high melting points and so they too are expected to exist in solution as coordinated aggregates which therefore resist N-quaternization. Moreover, the "ate" complex formed on addition of a trialkylborane to a lithiated hetarene made by lithium halogen exchange can be N-alkylated.[74] N-oxidized pyridyl boranes appear to be unknown.

The substitution of a boronic acid in place of a borane also has its severe limitations. The successful N-methylation of 3-pyridylboronic acid has only been reported recently; the method requires the use of an alkylating agent with a leaving group that is non-nucleophilic such as a sulfonate ion.[77] A reactive anion such as iodide from methyl iodide alkylating agent causes decomposition of the product.[77]

Figure 3-2



X= Cl, Br, I

M= BEt_2, $SnBu_3$

R= CH_3, O^-

In view of such limitations, we now employ a variation of the Stille reaction.[2,78] We use a hetarylstannane in place of the borane and N-oxidize or N-quaternize this organometallic compound instead of the halide, a so-called "reverse polarity" method. The palladium cross-coupling step is carried out in a nonaqueous solvents such as DMF, THF or toluene in order to reduce the possibility of hydrolytic side-reactions (Figure 3-2).

While many hetaryl stannane precursors are known substances,[50,79-86] their N-oxides and N-methyl derivatives are largely unknown compounds. Several are prepared and reported here for the first time. Stannylated 1-(alkoxycarbonyl)pyridinium ions have been generated but only as reactive intermediates.[87]

The scope and some of the limitations of the new method are illustrated by the following preparations. In many cases examples were selected to show how easy it is to prepare N-functionalized derivatives that otherwise would be difficult and tedious to prepare and purify by standard oxidation or quaternization reactions on the *preformed* polycyclic azine free base.

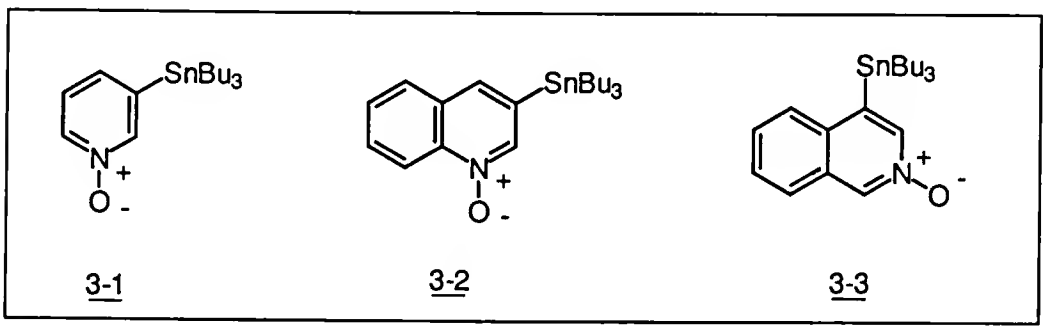
Three different stannylated heterocyclic rings were successfully cross-coupled. With the pyridine, quinoline and isoquinoline substrates the functionalized annular nitrogen atom is located in a 1,3 arrangement with respect to the stannylated site while the geometry is 1,4 for another pyridine. Special problems were encountered when attempting to N-methylate a 2-stannylated pyridine to provide a 1,2 geometry; coupling was not attempted.

The diverse group of five halogenated compounds included 3-bromoquinoline, 4-bromoisoquinoline, 5-bromopyrimidine, 3-iodopyridine, and 2-chloropyrazine. A total of 16 cross-coupled products exemplifying 11 different ring systems were prepared.

Results and Discussion

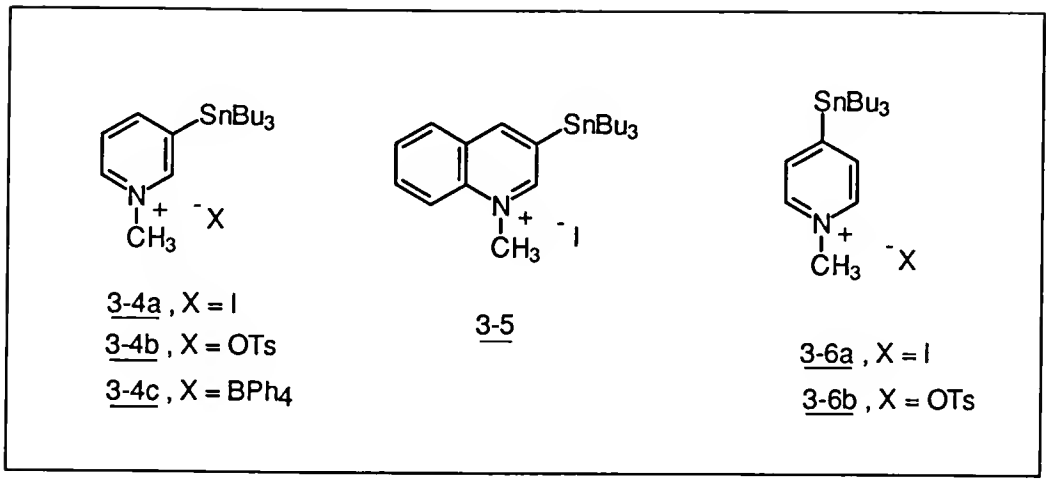
N-Oxidation and N-Methylation of Hetaryl Stannanes

3-(Tributylstannyl)-pyridine[79] and -quinoline[79] and 4-(tributylstannyl)isoquinoline were N-oxidized with m-chloroperbenzoic acid in chloroform to give the corresponding pyridyl 3-1 (88%), quinolyl 3-2 (88%), and isoquinolyl 3-3 (80%) N-oxides. Only the 4-(trimethylstannyl)[88,89] and 4-(triphenylstannyl) pyridines have been N-oxidized.[89]



3-1 3-2 3-3

N-Methylation of 3-(tributylstannyl)pyridine and quinoline went smoothly to give the respective N-quaternized 3-stannylpyridine 3-4 (a 100% iodide and b 90% tosylate) and 3-quinoline 3-5 (92% iodide). Similarly, the corresponding 4-stannylpyridine 3-6 (a 96% iodide and b 93% tosylate) was readily prepared. The N-methylation of 3-(trimethylstannyl) pyridine with MeI has been reported in patents.[90] Conversion of the iodide counter ion of 3-4a to the insoluble tetraphenylborate salt occurred easily on addition of $NaBPh_4$ to give 3-4c (97%).



In marked contrast, N-methylation of 2-(tributylstannyl)pyridine (CH_2Cl_2, 7 °C) could only be achieved with methyl triflate to give a labile product which was unstable at room temperature, giving rise to the destannylated N-methylpyridinium ion on standing. The material was, however, stable when kept below 0 °C but pure product was not isolated. The triflate salt immediately destannylated in DMSO to yield N-methylpyridinium ion. Attempts at quaternization using either methyl iodide or methyl tosylate proved to be unsuccessful. Cross-coupling was not attempted. No doubt a pyridinium ylide is generated on destannylation and the stability of this intermediate accounts for the facile decomposition.[91-93]

Cross-Coupling of Stannyl N-Oxides

Cross-coupling of pyridine N-oxide 3-1 in DMF containing $Pd(PPh_3)_4$ took place with 3-bromoquinoline to give N-oxide 3-7

and with 4-bromoisoquinoline to give N-oxide 3-8, Table I. Whereas the alternate synthesis of 3-7 might well be achieved by N-oxidation at the less sterically hindered nitrogen atom of the known preformed 3-(3-pyridyl)quinoline free base[67] this is not likely to be the case with the 4-(3-pyridyl)isoquinoline where both nitrogen atoms are expected to have very similar reactivities, making the preparation and isolation of 3-8 quite difficult by such a route. Moreover, in both cases, N-oxidization of preformed coupled bihetarene is likely to result in a mixture of mono- and di-N-oxidized products.[56]

Cross-coupling of pyridine N-oxide 3-1 with 5-bromopyrimidine in THF gave pyrimidine N-oxide 3-9. Similarly, quinoline N-oxide 3-2 and 4-isoquinoline N-oxide 3-3 on coupling with 5-bromopyrimidine in toluene afforded pyrimidine N-oxides 3-10 and 3-11, respectively, Table I. Again, in these three examples the efficient preparation of the final products 3-9, 3-10 and 3-11 from the preformed polyazine free bases such as the known[94] precursor of 3-9 is unlikely due to both steric and electronic factors which favor the formation of a mixture of isomers. In all these experiments the stannane served as the limiting reagent and the yields of the cross-coupled products were moderate (43-66%).

By contrast, when the limiting reagent was changed to the hetaryl halide as in the case of the coupling of 2-chlororpyrazine to stannylated N-oxide 3-1 present in excess,

the yield of coupled product 3-12 was essentially quantitative, Table I.

Table 3-1. Conditions and Results of the Cross-Coupling of Stannylated Hetaryl N-Oxides with Hetaryl Halides in the Presence of $Pd(PPh_3)_4$

Stannane	Halide[a]	Solvent/ time (h)	Product	% Yield
3-1	3Br	DMF/(24)	3-7	66
3-1	4Br	THF/20)	3-8	43
3-1	5Br	THF/(12)	3-9	64
3-2	5Br	toluene/ (18)	3-10	51
3-3	5Br	toluene/ (10)	3-11	58
3-1	2Cl	THF/(36)	3-12	98[b]

[a]3Br is 3-bromoquinoline, 4Br is 4-bromoisoquinoline, 5Br is 5-bromopyrimidine and 2Cl is 2-chloropyrazine.

[b] The limiting reagent in this one case is the halide and not the stannane.

Cross-Coupling of N-Methylated Stannanes with Stannane as the Limiting Reagent

Cross-coupling of N-methylated hetaryl stannanes proved to be more of a challenge than coupling of the N-oxides; the choice of the counter anion of the stannane salt was vitally important. Both iodide and tetraphenylborate ions proved to be unsatisfactory but for different reasons.

N-Methyl-3-tributylstannylquinolinium iodide 3-5 was coupled to 3-iodopyridine in the presence of $Pd(PPh_3)_4$ to give 3-13 (15%), Table II. The low yield seems to be a result of using the iodide as a counter ion. We have observed that such quaternized stannanes are easily destannylated by halide ions.

Table 3-2. Results of the Cross-Coupling of N-Quaternized Stannanes and Hetaryl Halides with Pd Catalysts Under Conditions of Molar Excess Halide (A) or Excess Stannane (B)

Stannane	Halide[a]	Catalyst (Method)	Solvent/ time(h)	Product	% Yield
3-5	3I	$Pd(PPh_3)_4$ (A)	THF/(18)	3-13	15
3-4C	5Br	$Pd(PPh_3)_4$ (A)	toluene/ (12)	3-14	55
3-4C	2Cl	$Pd(PPh_3)_4$ (A)	toluene/ (16)	3-15a	29
3-4C	$NaBPh_4$	Pd(dppe) Cl_2 (A)	THF/(10)	3-16	64
3-4b	3Br	$Pd(PPh_3)_4$ (A)	toluene/ (10)	3-17a	54
3-6b	3Br	$Pd(PPh_3)_4$ (A)	THF/(24)	3-18	54
3-6b	5Br	$Pd(PPh_3)_4$ (A)	toluene/ (30)	3-19	74
3-6b	3I	$Pd(PPh_3)_4$ (A)	DMF/(12)	3-20	64
3-4b	3Br	Pd(dppe) Cl_2 (B)	toluene/ (20)	3-17b	87
3-4b	2Cl	Pd(dppe) Cl_2 (B)	toluene/ (30)	3-15b	87
3-4b	4Br	Pd(dppe) Cl_2 (B)	toluene/ (24)	3-21	70
3-6b	4Br	Pd(dppe) Cl_2 (B)	toluene/ (30)	3-22	80

[a]3I is 3-iodopyridine, 5Br is 5-bromopyrimidine, 2Cl is 2-chloropyrazine, 3Br is 3-bromoquinoline and 4Br is 4-bromoisoquinoline.

Initially, in attempting to overcome competing destannylation the counter ion was changed from iodide to the less nucleophilic tetraphenylborate ion. Cross-coupling in the presence of $Pd(PPh_3)_4$ occurred between N-quaternized pyridine 3-4c and 5-bromopyrimidine to yield 3-14 in moderate yield (55%), Table II. Compound 3-4c was also found to couple to 2-chlororpyrazine to give 3-15a but in low yield (29%). It was discovered that it is essential to use a Pd(0) catalyst with tetraphenylborate as the counter ion in order to minimize competing phenylation by this anion. For example, in the presence of $Pd(dppe)Cl_2$, (dppe is 1,2-(diphenylphosphino) ethane) 3-4c and 5-bromopyrimidine gave only a small amount (10%) of the expected product 3-14 with the main product being 3-phenylpyridinium ion 3-16[69] (62%). The tetraphenylborate is known to be a phenylating agent.[95] In accordance with this, compound 3-4c in the presence of $Pd(dppe)Cl_2$ and one equivalent of $NaBPh_4$ gave 3-16 in 64% yield, Table II.

Tosylate was found to be the most useful counterion because it was inert. N-Quaternized pyridyl stannanes 3-4b and 3-6b with this anion were coupled to 3-bromoquinoline to give known 3-17[69] and 3-18, respectively. Note that 3-13 and 3-17 are isomers, site specific N-methylation having been achieved in each case. In addition, stannane 3-6b was coupled to 5-bromopyrimidine and to 3-iodopyridine to give 3-19 and 3-20, respectively, Table II. The presence of freshly prepared CuI[96] had no significant influence on the product ratio in the

coupling route providing 3-20. This salt is known to accelerate cross-coupling of stannanes by acting as a phosphine trap, thereby facilitating transmetallation.[28] An alternate synthesis of these compounds might be possible by selective quaternization of the coupled free base such as the known neutral precursor[58] of 3-18 but diquaternization is likely to be an important competing process especially in the case of the precursor[97] of 3-20 where steric and electronic differences between the two nitrogen atoms are minimal. In some instances it was prudent to convert the tosylate coupled product to a tetraphenylborate or perchlorate salt for easy isolation.

Cross-coupling of N-Methylated Stannanes with Hetaryl Halide as the Limiting Reagent

In all of the above cross-coupling reactions with N-oxidized and N-quaternized stannanes, the major side reaction is homocoupling of the stannane to give a di-N-oxidized or diquaternized material. Attempts to suppress homocoupling by degassing the system to remove dissolved oxygen as found by others[4,30] did not improve yields greatly by diminishing the amount of homocoupled side-product. It has been suggested that Pd(II) and not Pd(0) is responsible for homocoupling.[98] No attempts were made to recover these homocoupled products but their removal was quite simple. When the impurity was the highly insolubility diquaternized material, a simple

acetonitrile wash recovered the desired soluble product leaving the insoluble dication. The di-N-oxidized homocoupled product was removed easily on standard column chromatography.

When the hetaryl halide served as the limiting reagent and the stannane now was present in molar excess (2 to 2.5 equivalents), yields of the desired cross-coupling product improved significantly, Table II. For example, cross-coupling of pyridyl stannane 3-4b with 3-bromoquinoline and 2-chlororpyrazine in the presence of $Pd(dppe)Cl_2$ gave compounds 3-17b (87%) and 3-15b (87%), respectively, Table II. By contrast, 3-bromoquinoline and 2-chlororpyrazine under our previous conditions using the stannane as the limiting reagent gave these products in only 54% and 29% yield, respectively. In addition, N-methylated pyridines 3-4b and 3-6b were coupled to 4-bromoquinoline under similar conditions to give known compound 3-21[69] and 3-22, respectively. Thus, yields of cross-coupled products under conditions of excess stannane did increase, ranging from 70 to 87%, Table II. Again, the impurity was the homocoupled material.

Conclusions

Hetaryl stannanes N-functionalized in the form of N-oxides or N-quaternized salts cross-couple with hetaryl iodides, bromides, and chlorides with little or no change in yields. Due to their ease of preparation, N-functionalized

stannanes, in contrast with boranes, are the reagents of choice for a cross-coupling reaction in which the organometallic component is N-functionalized. When a quaternized hetaryl stannane is employed, it is advisable to select an inert tosylate ion as the counteranion of the salt.

The examples shown here reveal the power of the new synthetic method whereby an annular nitrogen atom is functionalized prior to cross-coupling. In this way the structure of the N-oxide or N-quaternized coupled product is both obvious and assured.

Clearly, our approach may be applied to rings of other size and construction and to the introduction of other substituents onto an annular nitrogen atom. The scope seems to be wide and the method useful. The coupled products themselves may serve as starting materials. The N-functional groups provide a special chemistry that directs new substituents to their activated ring and thereby allow further controlled elaboration.[99-103]

CHAPTER 4
N-METHYLATION AND N-OXIDATION OF THE LESS REACTIVE NITROGEN ATOM OF A 2,3′-BIPYRIDINE--TWO GENERAL METHODS FOR POLYAZINES

Introduction

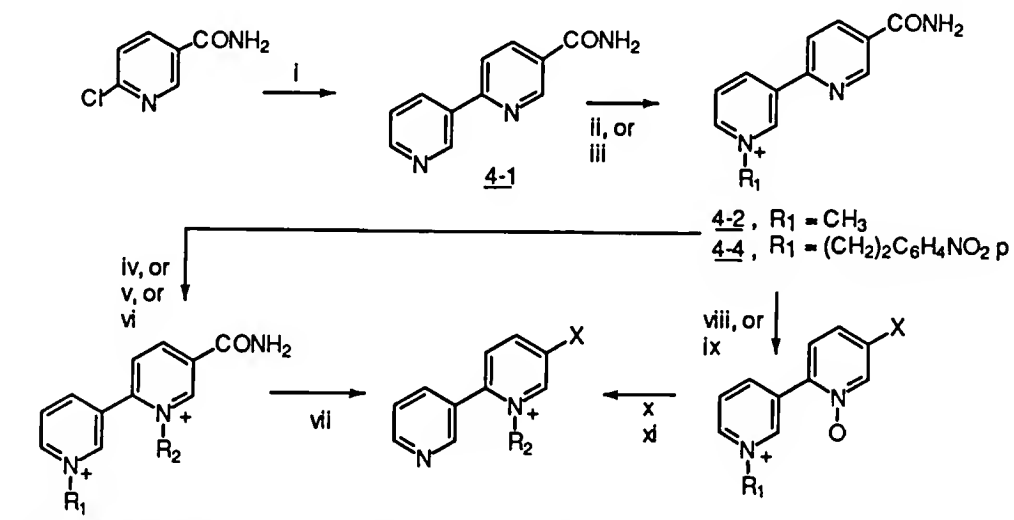
Directing a reaction to one selected annular nitrogen atom of a polyazine or a polycyclic polyazine is an old and continuing synthetic challenge. Especially difficult is the case where the desired reaction site is sterically hindered and/or electronically deactivated.

2,3′-Bipyridine is a prototypical polyazine where the two annular nitrogen atoms demonstrate markedly different reactivities due to their geometry, the nitrogen atom of the 2-pyridyl ring being more sterically hindered and therefore much less nucleophilic than that of the 3′-pyridyl ring.

We have devised two different methods to achieve regiocontrolled functionalization of one annular nitrogen atom using a 2,3′-bipyridine as a model substrate. When it is desirable to functionalize the less reactive nitrogen atom in the 2-pyridyl ring of the 2,3′-bipyridine our first approach employs a three-step protection-functionalization-deprotection sequence on *preformed* 2,3′-bipyridine. A removable 2-(p-nitrophenyl)ethyl (NPE) protecting group is first bonded to the more reactive 3′-pyridyl nitrogen atom, the less reactive

2-pyridyl nitrogen atom then is functionalized by N-quaternization or N-oxidation and the protecting group is removed by base as p-nitrostyrene to give the desired final product. A simpler approach for the N-oxide employs an N-methyl protecting group, readily removed by the action of KI in heated DMF in a similar sequence of steps (Figure 4-1).

Figure 4-1[a]

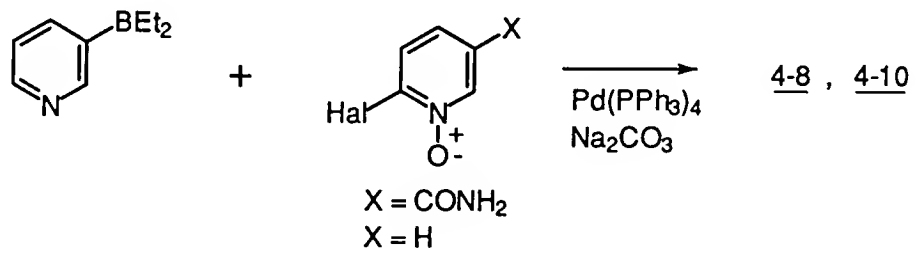


[a]Reagents: (i) $Pd(Ph_3)_4$, 3-Et_2B-pyridine, THF, (ii) MeI, EtOAc, (iii) $Br(CH_2)_2C_6H_4NO_2$, (iv) MeI, DMF, (v) MeI, sulfolane (vi) MeOTs, sulfolane, (vii) NaOAc, MeCN for 4-5, (viii) MCPBA, sulfolane for 4-7; peroxide, TFA for 4-9, (ix) MCPBA, $CHCl_3$ for 4-11, (x) NaOAc, MeCN for 4-7, (xi) KI, DMF for 4-9 and 4-11.

In the second method the desired nitrogen atom is functionalized *first* and *then* the two pyridine rings are cross-coupled together to generate the BPY using a palladium

catalyst, a pyridyl borane and an N-oxidized halogenated pyridine (Figure 4-2).

Figure 4-2



Our model substrate selected to illustrate these two methods is 5-carbamoyl-2,3′-bipyridine (4-1). Not only is the 2-pyridyl ring sterically deactivated for nucleophilic reactions but also the carbamoyl group presents substantial additional electronic deactivation. The 2-pyridyl ring in 4-1 is so deactivated that we were forced to devise new reaction conditions which differ markedly from those used in the first successful synthesis of 1-methyl-2,3′-bipyridinium ion.[104] The new conditions are likely to be more widely applicable to other substrates.

The regiocontrolled N-methylation of 4-1 at the 2-pyridyl nitrogen atom to give 4-6 and the regiocontrolled N-oxidation of the 2-pyridyl nitrogen atom of 4-1 to prepare 4-8 were achieved by the first route.

Using the second synthetic approach N-oxide 4-8 also was prepared but the cross-coupling route failed to provide N-methylated 4-6.

Results and Discussion

Pd-Catalyzed Cross-Coupling

Bipyridine 4-1 was readily prepared (92%) by a Suzuki[3,43,44,46] cross-coupling of diethyl(3-pyridyl)borane and 2-chloro-5-carbamoylpyridine with tetrakis- (triphenylphosphine) palladium(0) and an aqueous carbonate buffer. The 5-methyl ester has been made by a similar route[67] but the isomeric 2-chloro-3-carbamoylpyridine did not couple with benzeneboronic acid in the presence of $Pd(dppb)Cl_2$.[65]

N-Methylation

Mono- and di-N-methylation of 4-1 was examined to obtain information about the reactivity of the two nitrogen atoms and, as seen below, to learn about the thermal instability of the diquaternized salt toward demethylation. The first N-methylation took place readily to provide 4-2, 1'-methyl-5-carbamoyl-2,3'-bipyridinium iodide in 80% yield with MeI and 99% yield with methyl tosylate (MeOTs).

The conditions selected for the second N-methylation were dictated by the limited solubility of 4-2, its diminished reactivity and subsequent thermal dequaternization. Our

conditions used for the preparation of the diquaternized form of BPY itself, MeI in acetonitrile heated at 100 °C in a sealed tube,[104] were unsatisfactory. Sulfolane solubilized monocation 4-2 and heating with excess MeOTs at 110 °C gave (4-3), 1,1′-dimethyl-5-carbamoyl-2,3′-bipyridinium ion (84%). Heated DMF and MeI was unsatisfactory because a mixture of mono (4-2) and diquaternized (4-3) products along with tetramethylammonium solvent decomposition product were isolated in low yields.

Addition of the Protecting Group and Diquaternization

The addition of the NPE protecting group to N-1′ was achieved easily in 90% yield to provide monocation 4-4.

Again, the second methylation step was a challenge. The solvent of choice proved to be sulfolane because of its good solvent properties and its inertness to the methylating agent. However, the yield of desired diquaternized 4-5 was only 15% using MeI because deprotection of the starting material by iodide ion followed by methylation to form dimethylated dication 4-3 was a competing process. Reverse phase column chromotography[105] proved useful in the separation of materials.

The yield of 4-5 improved to 85% with MeOTs. No dequaternization now was evident with the weakly nucleophilic tosylate counterion.

Attempts to attach other groups to N-1 of 4-4 were unsuccessful. Neither ethyl tosylate nor bromoacetonitrile nor

benzyl bromide, the latter in the presence of silver salts,[106] could be made to react, providing further evidence of the markedly low reactivity of this atom.

An attempt was made to bond a 2-cyanoethyl group to the N-1′ atom of 3-1 with the expectation that it would be easier to remove by the action of base in the deprotection step.[107,108] However, the 2-cyanoethyl bromide alkylating agent only gave rise to low yields of the desired N-quaternized product.

Deprotection

Selection of conditions for the successful removal of the N-protecting group required several trials. The 2,2,6,6-tetramethylpiperidine base used in our earlier study[104] was unsatisfactory because of the difficulty encountered in removing it as its tosylate salt from the desired ionic product 4-6, 1-methyl-5-carbamoyl-2,3′-bipyridinium ion. Dry sodium acetate in refluxing acetonitrile brought about the elimination of 4-nitrostyrene to regenerate the unsubstituted 3′-pyridyl ring and the monomethylated product 4-6 (55%).

N-Oxidation

(Nitrophenyl)ethylated material 4-4 was easily N-oxidized to 4-7 using 3-chloroperbenzoic acid[99] in sulfolane (57%) and the protecting group was removed using sodium acetate in acetonitrile to yield 5-carbamoyl-2,3′-bipyridine-1-oxide 4-8 (62%).

In view of the easy dealkylation of 4-3 by iodide ion, another route was explored, now using the N-methyl substituent on N-1′ as a protecting group. Iodide 4-2 was first converted to the tosylate at room temperature with MeOTs to generate volatile MeI in an anion exchange reaction in order to avoid oxidizing the iodide counterion and then N-oxidized (86%) in peroxytrifluoroacetic acid[109] to 5-carbamoyl-1′-methyl-2,3′-bipyridinium-1-oxide (4-9). Deprotection, this time removing the methyl group using KI in heated DMF, gave the more sterically hindered mono N-oxide 4-8 (55%).

On the parent bipyridine lacking the carbamoyl substituent, the same sequence of N-1′ protection with a methyl group followed by N-oxidation gave 4-11 which then was deprotected thermally with KI in hot DMF to afford 4-10 (40%). N-oxidation of unprotected bipyridine has been reported along with spectroscopic properties.[56,110]

Palladium-Catalyzed Coupling to Prepare N-Oxide 4-10

A more direct route to 4-10 (68%) employed palladium-catalyzed cross-coupling[3,43,44,46] of diethyl(3-pyridyl)borane and 2-bromopyridine-1-oxide in aqueous carbonate. Although the 2-bromopyridine-1-oxide can undergo a facile nucleophilic substitution reaction with hydroxide ion to give a pyridone,[52] this side-reaction was not important. A 2-bromopyridine-1-oxide has been made to couple with a thienylboronic acid under similar conditions.[47]

Palladium-Catalyzed Coupling to Prepare N-Oxide 4-8

6-Chloro-nicotinamide was N-oxidized with urea-H_2O_2 complex and triflouroacetic acid to give the N-oxide (86%). Coupling with diethyl(3-pyridyl)borane, Pd(0) and carbonate gave 4-8 in 73% yield (Figure 4-2).

Unsuccessful Palladium-Catalyzed Coupling to Prepare 4-6

Our ability to cross-couple diethyl(3-pyridyl)borane with N-methylated pyridinium, quinolinium and isoquinolinium halides having the halogen atom located beta to the annular nitrogen atom[79] encouraged us to attempt the preparation of 4-6 by such a route using a quaternized substrate having the halogen atom at an alpha position. Unfortunately, all attempts failed. Thus, coupling of the 3-pyridylborane and 2-bromo-1-methylpyridinium ion was unsuccessful using carbonate or bicarbonate buffers and tetrakis(triphenylphosphine) palladium(0) or $Pd(dppe)_2Cl_2$ (dppe is 1,2-(diphenylphosphino) ethane).

Switching to 3-(tributylstannyl)pyridine and 2-bromo-1-methyl pyridinium under non-aqueous conditions (Stille-type conditions) also failed to give any coupled product. A variety of solvents (THF, dioxane, and DMF) and catalysts ($Pd(PPh_3)_4$, $Pd(dppe)_2Cl_2$ and Pd_2dba_3) were tried with no success.

Conclusions

The NPE group is useful to protect[111] an annular nitrogen atom of a preformed polycyclic azine where it can be removed subsequently as 4-nitrostyrene in the presence of a base such as acetate ion. The deprotection pathway allows for regiospecific preparation of N-derivatized compounds having substituents on the less reactive annular nitrogen atom of polyaza compounds. For N-oxides, an N-methyl substituent is an attractive alternate protecting group readily removable by thermally induced nucleophilic substitution with iodide ion.

The two methods for the preparation of carbamoyl N-oxide 3-8 may be compared, each ultimately starting with the 3-pyridylborane and a 2-halopyridine. The two-step palladium coupling route first making the N-oxide and then coupling the two reactants is shorter and gives 4-8 in 63% overall yield. The four-step sequence where the 2,3-bipyridine is prepared first by palladium coupling, protected, N-oxidized and then deprotected gives an overall yield of 29% for the route using the NPE protecting group and 43% for the methyl protection scheme. Although unsubstituted N-oxide 4-10 was synthesized by the two routes the starting points are not the same for both approaches to allow a meaningful comparison. The overall yield for the four-step route to the N-methylated carbamoyl 4-6 was 39%.

Our two methods would seem to be useful for the preparation of a variety of selectively N-derivatized polyazines. If the construction of an inter-ring bond to make a polycyclic structure is an option, then functionalizing an annular nitrogen atom of an azine prior to palladium-catalyzed cross-coupling serves as a useful shorter second route to regiospecifically N-functionalized polycyclic polyazines. However, while this approach was successful for the synthesis of an N-oxide it failed here for an N-quaternized azine having the halide group located alpha to this nitrogen. For the later compounds, the first method using a protecting group on preformed polycyclic polyazines remains the method of choice.

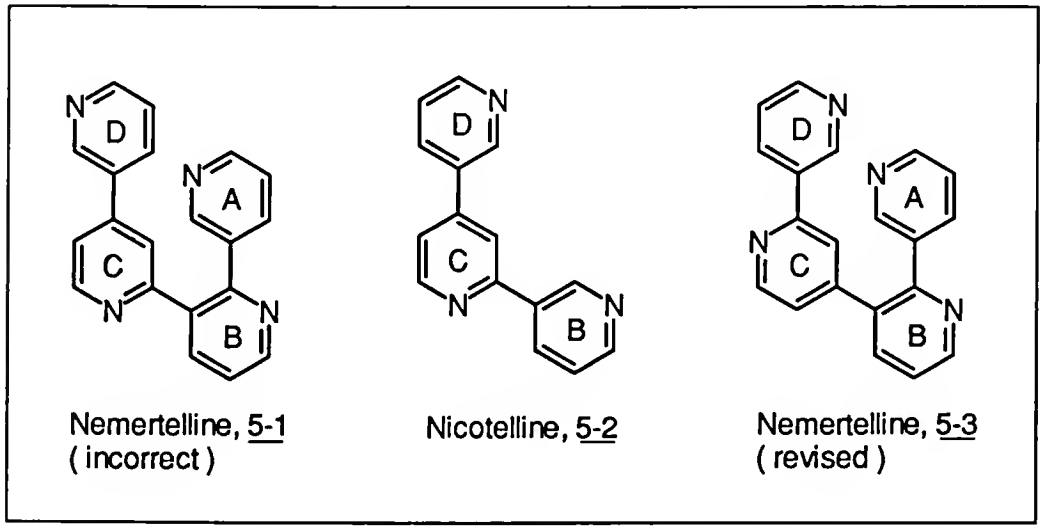
CHAPTER 5
REVISED STRUCTURE AND CONVERGENT SYNTHESIS OF THE NEUROTOXIC QUATERPYRIDINE ISOLATED FROM THE HOPLONEMERTINE SEA WORM.

Introduction

Neurotoxic substances have been isolated from the phylum of marine worms called nemertines. Extracts from the hoplonemertine (armed) worm contain anabaseine (3,4,5,6-tetrahydro-2,3′-bipyridine), 2,3′-bipyridine and a quaterpyridine given the name nemertelline (3,2′:3′,2′′:4′′,3′′′-quaterpyridine, 5-1). The proof of structure of this first quaterpyridine isolated from a living source rested in 1976 entirely on its 90 MHz proton NMR spectrum, homonuclear decoupling experiments, and the similarity of the proton NMR spectrum to that of nicotelline.[41] Nicotelline (5-2), a tripyridyl tobacco alkaloid, also contains the B-C-D ring structure present in 5-1, but lacks ring A. The proton NMR spectrum of nicotelline is strikingly similar to the proton resonances assigned to rings A, C, and D of the natural product.[41]

The synthesis of this unsymmetrically substituted quaterpyridine seemed to us to be readily possible given the recent development of palladium-catalyzed cross-coupling reactions allowing for the easy construction of carbocyclic

and heterocyclic polyaromatic substrates from organometallic and halide precursors. Suzuki coupling of boranes or borates[3,44,69-71] and Stille coupling of stannanes[2,43,78,84,112,113] now are the preferred methods of joining such rings.



We now report the first synthesis of 5-1 and its correct proton NMR spectrum. Spectral differences between this synthetic quaterpyridine and that of the natural substance clearly indicate that 5-1 is not the natural product. The correct structure of the natural product nemertelline is 3,2′:3′,4′′:2′′,3′′′-quaterpyridine (5-3) which is verified by an independent synthesis involving a key palladium-catalyzed cross-coupling step. The two isomers differ only in the location of the nitrogen atom in the 2,4-disubstituted C-ring. Both substances consist of two 3-substituted pyridyl rings along with 2,3- and 2,4-disubstituted pyridine rings.

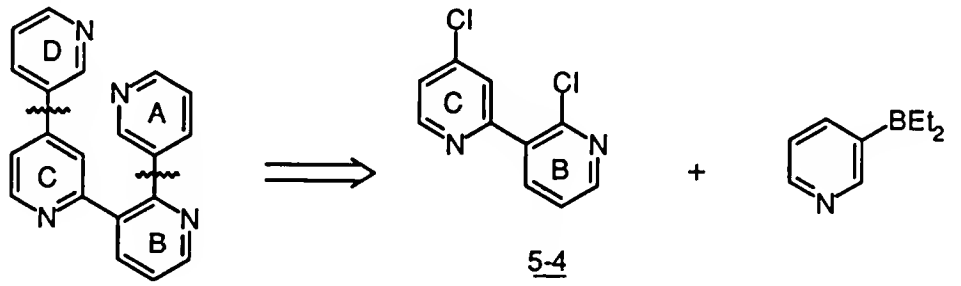
The natural product nemertelline (5-3) is an unsymmetrical dimer of 2,3′-bipyridine.

Results and Discussion

Synthesis of 3,2′: 3′,2′′:4′′,3′′′-Quaterpyridine (5-1)

Our two retrosynthetic approaches for 5-1 are given in Figures 5-1 and 5-2. Both are predicated on the use of palladium-catalyzed cross-coupling[2,43,70] of organometallic and halide hetarenes to form bipyridine (bpy) rings.

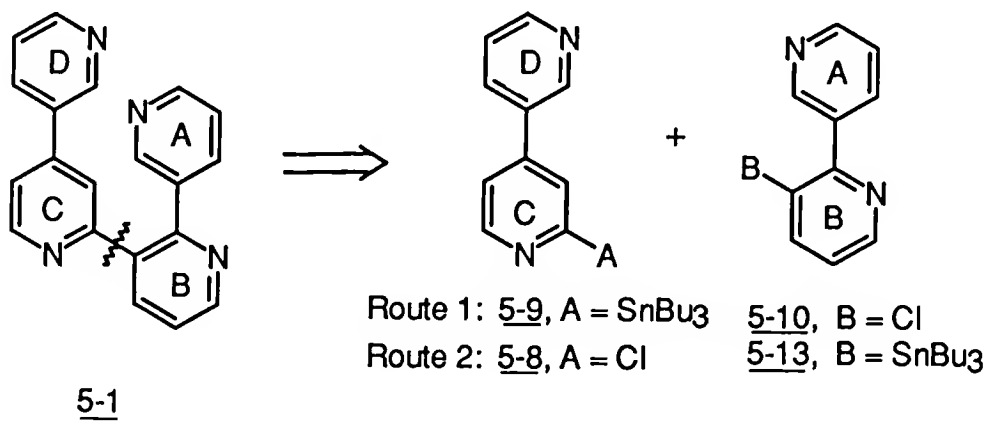
Figure 5-1: Retrosynthetic Analysis for Quaterpyridine 5-1



According to successful Figure 5-1 the two 3-pyridyl rings of 5-1 are disconnected from the central B-C rings, a 2,3′-bpy, to give its dichloride 5-4 and a 3-substituted pyridine, here used as its commercially available borane, diethyl(3-pyridyl)borane.

In Figure 5-2 the disconnection is made between the B and C rings to give two different bpy rings, 3,4′-bpy (A) containing the C-D rings and 2,3′-bpy (B) having the A-B rings. The polarity of this disconnection was reversed in our two approaches. In route 1 the C-D rings contain the organometallic stannane and the A-B rings the chloride. In route 2 the positions of the stannyl and chloro groups are reversed.

Figure 5-2: Retrosynthetic Analysis for Quaterpyridine 5-1



Although both routes in Figure 5-2 gave some of the desired quaterpyridine on cross-coupling, the material was contaminated with a homocoupling by-product that proved difficult to remove. The synthetic sequence in Figure 5-1 therefore is preferred.

In all the approaches the individual bpy rings were constructed by a palladium-catalyzed union of two pyridine rings.

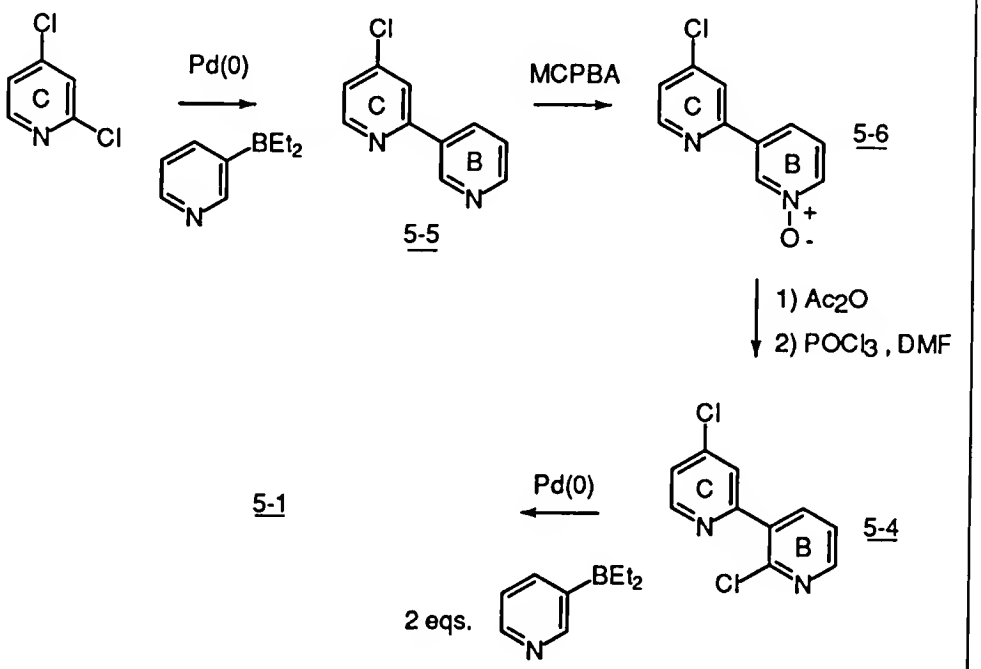
Retrosynthetic Figure 5-1: 2,4-Dichloropyridine, made from 4-nitropyridine N-oxide[114], was coupled with diethyl(3-pyridyl)borane under Suzuki conditions (Figure 5-3). Coupling took place at the 2 and not the 4-position of the dichloride to give 4-chloro-2,3′-bipyridine (5-6) (57%). There is a clear preference for coupling at the 2- over the 4-position in the 2,4-dichloride. But as the 4-chloro bipyridine product formed in large quantities, this product began to compete with the starting material in the coupling reaction to yield a known terpyridine (3,2′:4′3′′-terpyridine, nicotelline[97]). The coupling reaction was readily followed by silica gel TLC and was stopped when the terpyridine started to appear.

The structure of the 4-chlorobipyridine (5-5) was easily established by making assignments based on the large deshielding effect of an interannular nitrogen atom. The singlet of H-2 and the doublet of H-4 of the 3′-pyridyl ring of this bipyridine are highly deshielded, being at 9.33 and 8.34 ppm, respectively.

Monochloro 5-5 was selectively N-oxidized with MCPBA at the less sterically hindered nitrogen atom to form 5-6. Using known chemistry,[56] it was possible to convert this N-oxide to the 4-chloro-2,3′-bipyrid-2′-one with acetic anhydride. This pyridone then was transformed to 5-4 with $POCl_3$ and

DMF. Use of $POCl_3$ directly on the N-oxide is expected to give a mixture of two chlorinated isomers.

Figure 5-3

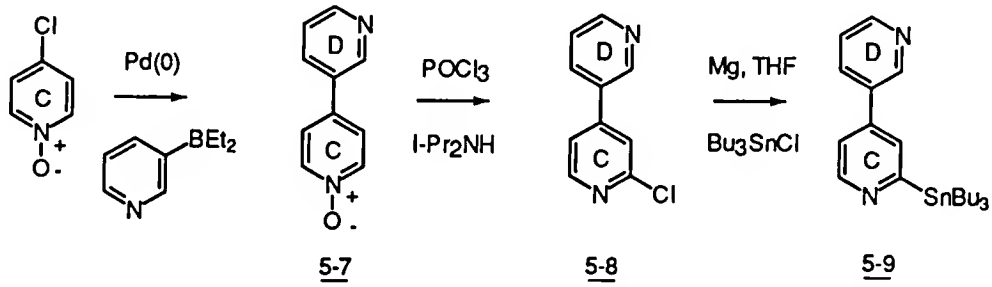


The final Suzuki coupling with slightly more than two equivalents of diethyl(3-pyridyl)borane and dichloride 5-4 provided 5-1 in 64% yield.

Retrosynthetic Figure 5-2, Route 1: The C-D ring system was made quite easily using chemistry recently developed by our group to provide regioselectively N-functionalized bpy rings.[69] In Figure 5-4, cross-coupling of 4-chloropyridine N-oxide and diethyl(3-pyridyl)borane under Suzuki-type conditions gave 3,4′-bipyridine N-oxide (5-7) in

good yield (75%). This material then was converted to 5-8 (A = Cl) with $POCl_3$ and diisopropyl amine followed by conversion to the Grignard reagent and transmetalation with tributyltin chloride. 2′-Tributylstannyl 5-9 was formed in moderate yield (34%).

Figure 5-4



5-7 5-8 5-9

The required 3-chloro-2,3′-bipyridine (5-10) was easily constructed from 2,3-dichloropyridine (92%) and the diethyl(3-pyridyl)borane under Suzuki conditions. Cross-coupling of the 2,3-dichloropyridine at the 2 and not the 3 position was easily demonstrated from the proton NMR spectrum by making use of the large deshielding effect of the annular nitrogen atom of the B ring on the 3′-pyridyl A ring. To verify that it was possible to cross-couple to the sterically hindered 3-Cl position of this bpy, a model coupling with diethyl(3-pyridyl)borane was attempted. The expected new 3,2′: 3′,3′′-terpyridine (5-11) was isolated in 62% yield indicating that the coupling reaction with the borane is not sensitive toward steric hindrance.

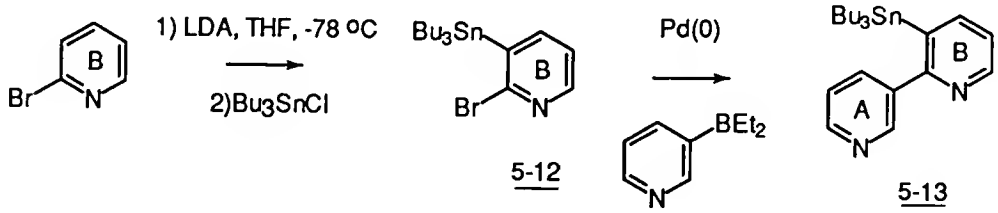
The final coupling to give 5-1 was carried out under typical Stille conditions using tetrakis(triphenylphosphine) palladium(0) and refluxing toluene. Unfortunately, an inseparable mixture of 5-1 and the homocoupled product of stannane 5-9 could not be easily separated by silica gel chromotography.

Retrosynthetic Figure 5-2, Route 2: In order to suppress homocoupling, the polarities of the bpy rings were reversed.

Two approaches were tried, only one being successful. In the successful approach the organometallic group was first added to the B-ring and then the A-ring was joined. In unsuccessful attempts this sequence was reversed. The A and B-rings were first bonded together and attempts then were made unsuccessfully to add an organometallic group to the B-ring of the bipyridine.

Taking advantage of known chemistry,[115-118] directed ortho lithiation of 2-bromopyridine with LDA at -78 °C followed by transmetalation with tributyltin chloride gave 2-bromo-3-tributylstannylpyridine (5-12) (57%). This stannane was easily coupled with diethyl(3-pyridyl)borane in the presence of tetrakis(triphenylphosphine)palladium(0) in THF under the usual aqueous alkaline Suzuki conditions to give 86% of 3-tributylstannyl-2,3'-bipyridine (5-13). Significantly, no destannylation took place under the conditions of the aqueous coupling (Figure 5-5).

Figure 5-5



In the alternate route a number of attempts to metallate the A-B ring of 3-halo-2,3′-bipyridine were tried. All attempts to convert the monochloride to the metallated material failed to give a substantial amount of the product. Thus, attempted transmetalation with n-BuLi at low temperatures (-78 and -100 °C) yielded minimal amounts of lithiated product along with butylated addition product.[119] Attempted Grignard formation from the chloride provided mostly 2,3′-bipyridine reduction product. Tributylstannide ion and the chloride gave only 10% of the 3-stannane. Use of the more reactive 3-bromo-2,3′-bipyridine (5-14) made from the corresponding 3-amine 5-15 in place of the 3-chloride did not change the outcome significantly.

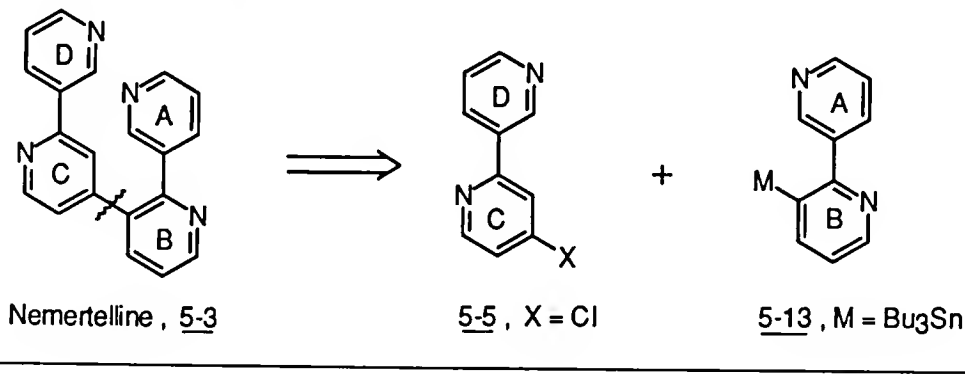
The coupling of chloride 5-8 (A = Cl) and stannane 5-13 (B = Bu_3Sn) again gave an inseparable mixture of 5-1 and a homocoupled product, that from 5-8.

Synthesis of Nemertelline (5-3)

Our retrosynthetic analysis of nemertelline in Figure 5-6 suggests a convergent synthesis in which the B and C rings are

disconnected to give the A-B and C-D bipyridyl rings as fragments. We elected to have the A-B fragment serve as the organometallic component and the C-D portion as the halide. In the reversed polarity approach in which the A-B fragment is the halide and the C-D unit contains the organometallic group there is the risk that the desired cross-coupling might fail. Such a cross-coupling is sterically hindered while the homocoupling of the stannane, a common side-reaction in Stille coupling,[4,98,120-122] is not so hindered and therefore might dominate. In our favored approach homocoupling of the stannane is a more sterically hindered process than cross-coupling.

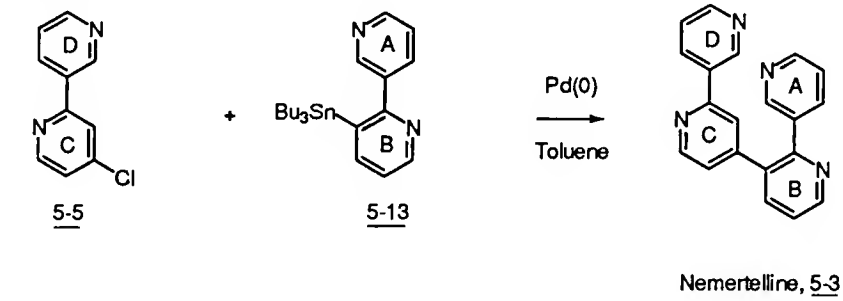
Figure 5-6: Retrosynthetic Analysis for Nemertelline, 5-3



Nemertelline, 5-3 | 5-5, X = Cl | 5-13, M = Bu_3Sn

Stille Coupling to give 5-3: The two bipyridines 5-13 and 5-5 were smoothly cross-coupled with Pd(0) catalyst in heated toluene to give 5-3 in 68% yield as demonstrated by both proton NMR and X-ray analysis of the product (Figure 5-7).

Figure 5-7



Crystal Structure of Nemertelline (5-3)

An X-ray analysis of the monoclinic crystals was obtained in order to confirm the structure of the natural product and thereby aid in the analysis of the NMR spectrum, Figure 5-8. The molecule is folded into a nonplanar approximate U-shape with, as expected from the structures of related polypyridines,[37,39,123,124] the orientation of the annular nitrogen atoms in adjacent rings adopt an s-trans conformation with respect to each other. The A and C rings are approximately parallel to each other and are skewed with respect to the common B ring. The dihedral angle between the rings is 44° for the A and B portion, 53° for the B and C rings and -23° for the C and D group. The D ring is twisted away from the A ring in the opposite direction from that of the A and C rings. The geometry of the A, B and C rings is similar to that of 1,2-diphenylbenzene.[125]

Proton NMR of 5-3: Comparison of the proton NMR spectrum of our synthetic nemertelline (5-3) with that of the natural quaterpyridine[41] indicates they are identical, thus providing

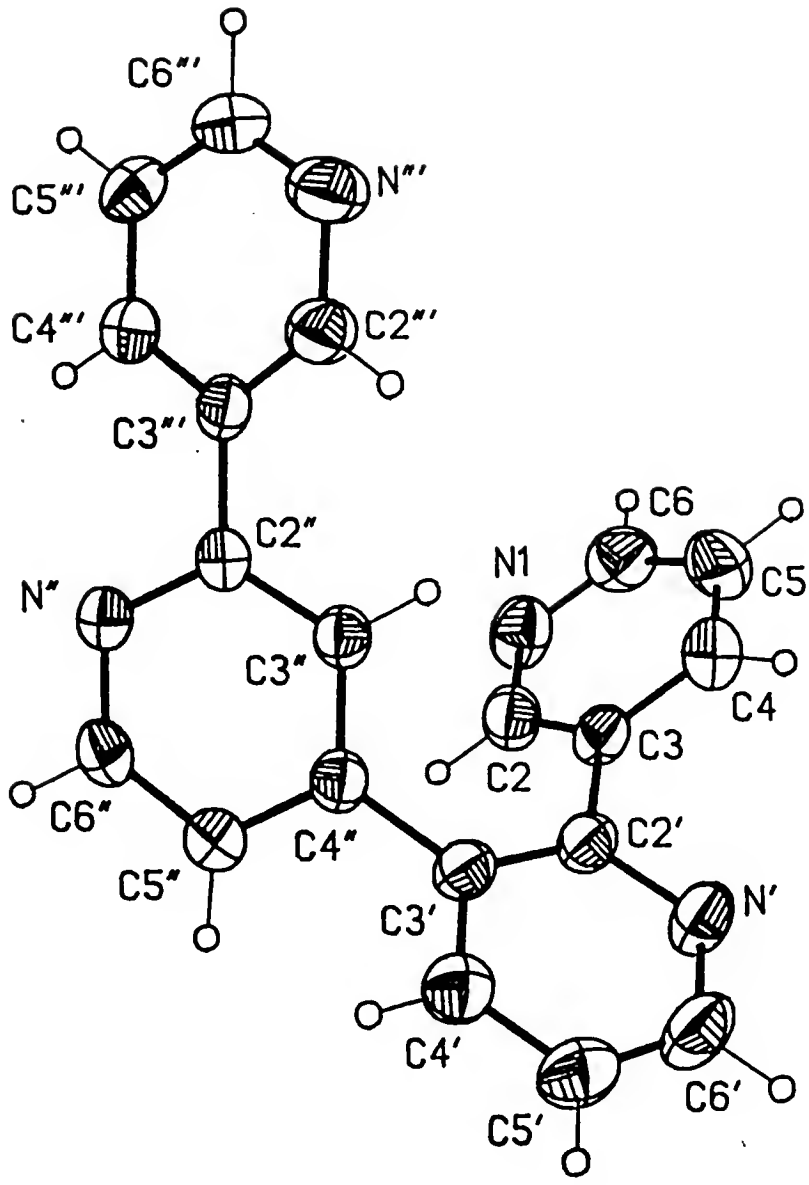


Figure 5-8. ORTEP crystal structure of nemertelline (5-3) with 50% probability ellipsoids.

(Courtesy of Dr. K. A. Abboud)

the final proof of structure. The early report used CS_2 as a solvent.[41] We find little difference in the spectra using this solvent or $CDCl_3$. The 300 MHz NMR spectrum of 5-3 in $CDCl_3$ with peak assignments is shown in Figure 5-9. Some signal overlap for three protons does occur in $CDCl_3$ at 8.6 ppm. Remarkably, none of the 14 aromatic protons overlap at 300 MHz in CD_3OD where the total shift scale is only 1.7 ppm, Figure 5-10.

The assignments are based on COSY and NOE difference spectra as well as the general pattern of chemical shifts and spin couplings observed for polypyridines. For each ring the signals usually follow an α, γ and β positional order (increasing magnetic field) as modified by the additional deshielding caused by the lone electron pair of an interannular nitrogen atom[40,126] as well as a shielding effect of stacked rings[127,128] as in the case of the A and C rings.

The COSY of 5-3 in $CDCl_3$ is given in Figure 5-11 where the proton assignment of the two important 3-pyridyl rings is emphasized. Significantly, one of these two rings has a pair of signals at 9.01 and 8.19 ppm which are located at much lower field than those for equivalent positions of the other ring. These deshielded protons are easily identified as being α and γ to a nitrogen atom by their spin coupling pattern. Moreover, irradiation of this α proton at 9.00 ppm gave rise to an NOE difference signal for proton 3'' of the C ring at 7.55 ppm while irradiation of the γ signal at 8.19 ppm caused an NOE to appear for the same 3'' proton. Thus, this pair of

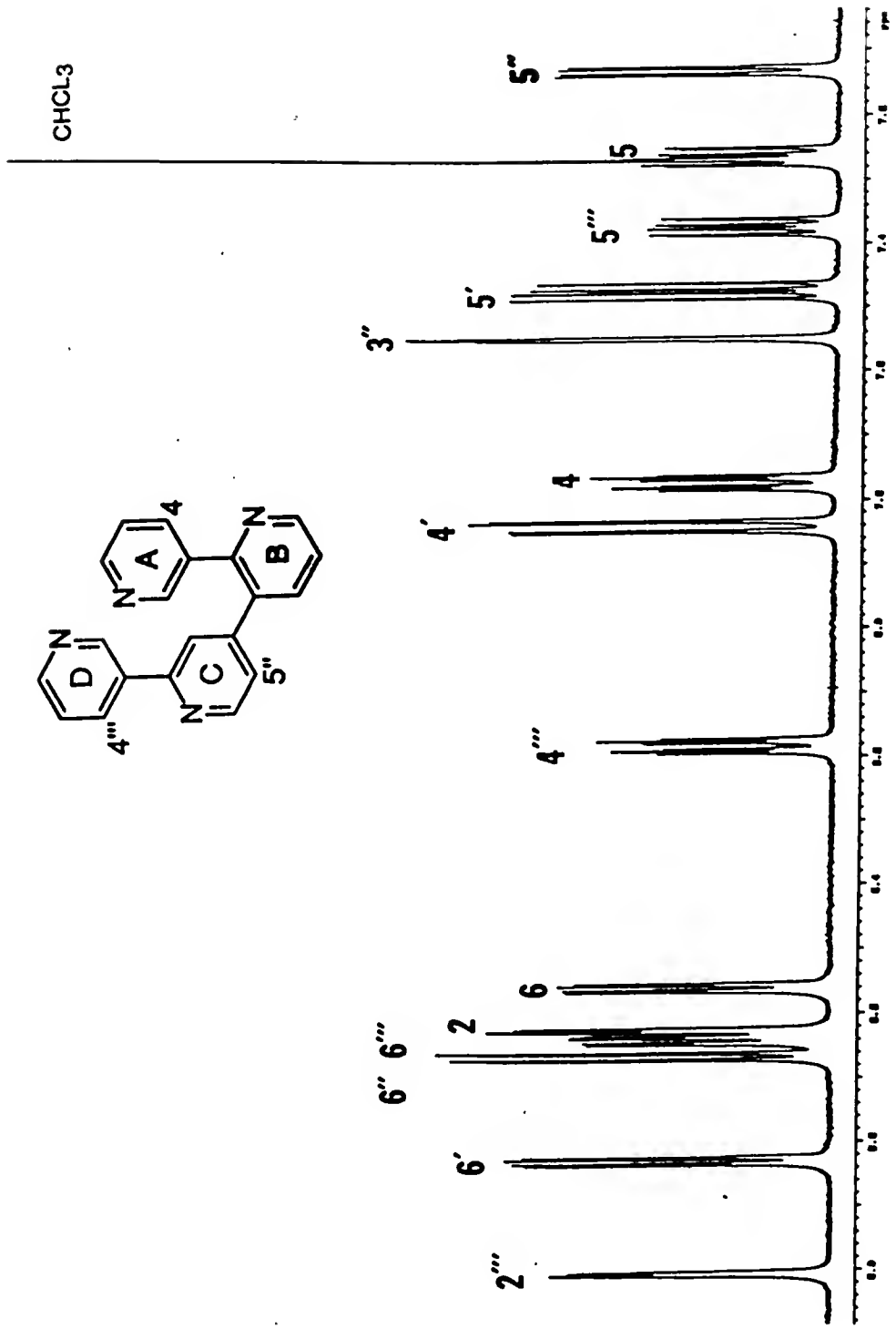


Figure 5-9

Proton NMR spectrum (300 MHz) of nemertelline (5-3) in $CDCl_3$.

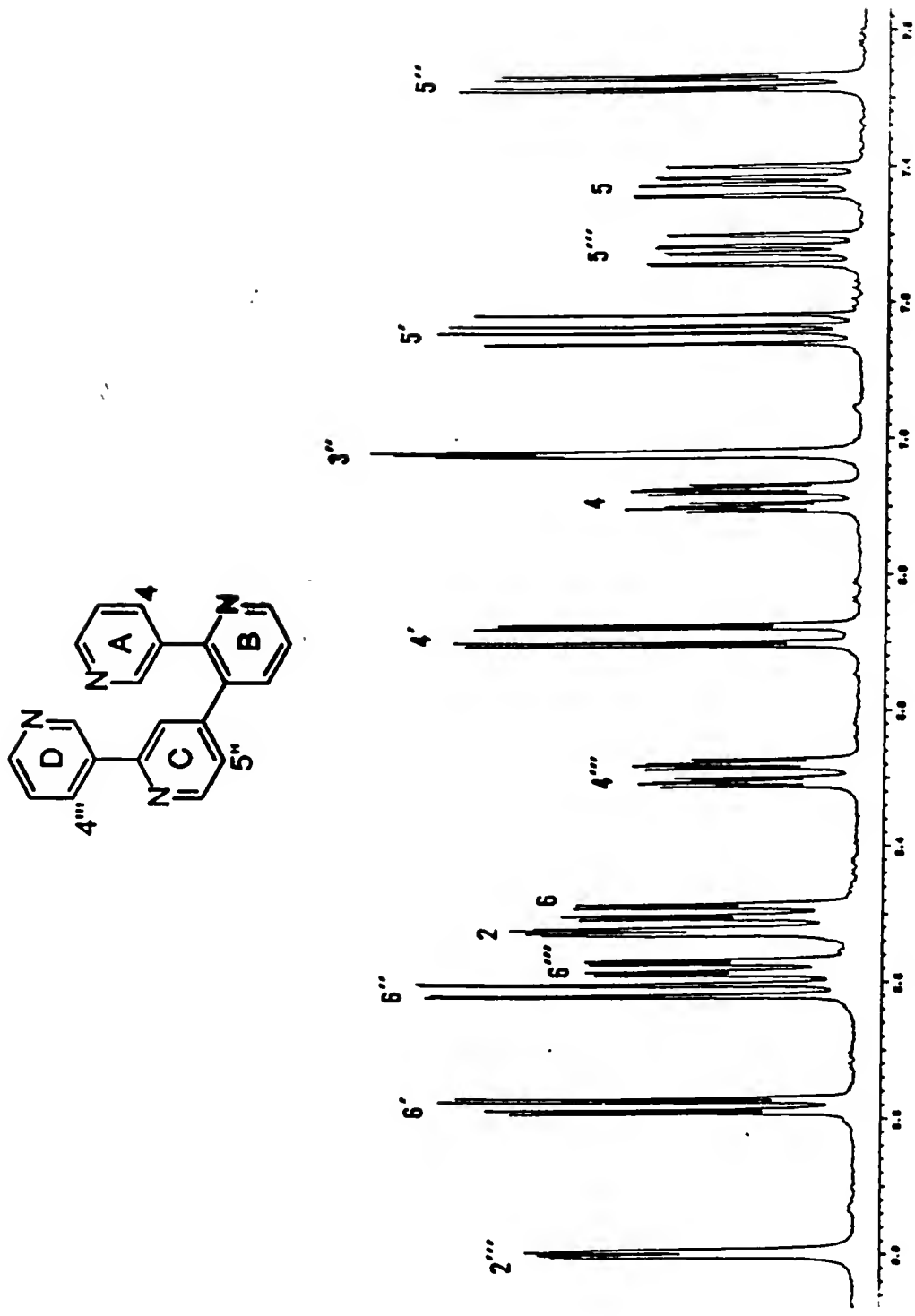


Figure 5-10

Proton NMR spectrum (300 MHz) of nemertelline (5-3)

in CD_3OD.

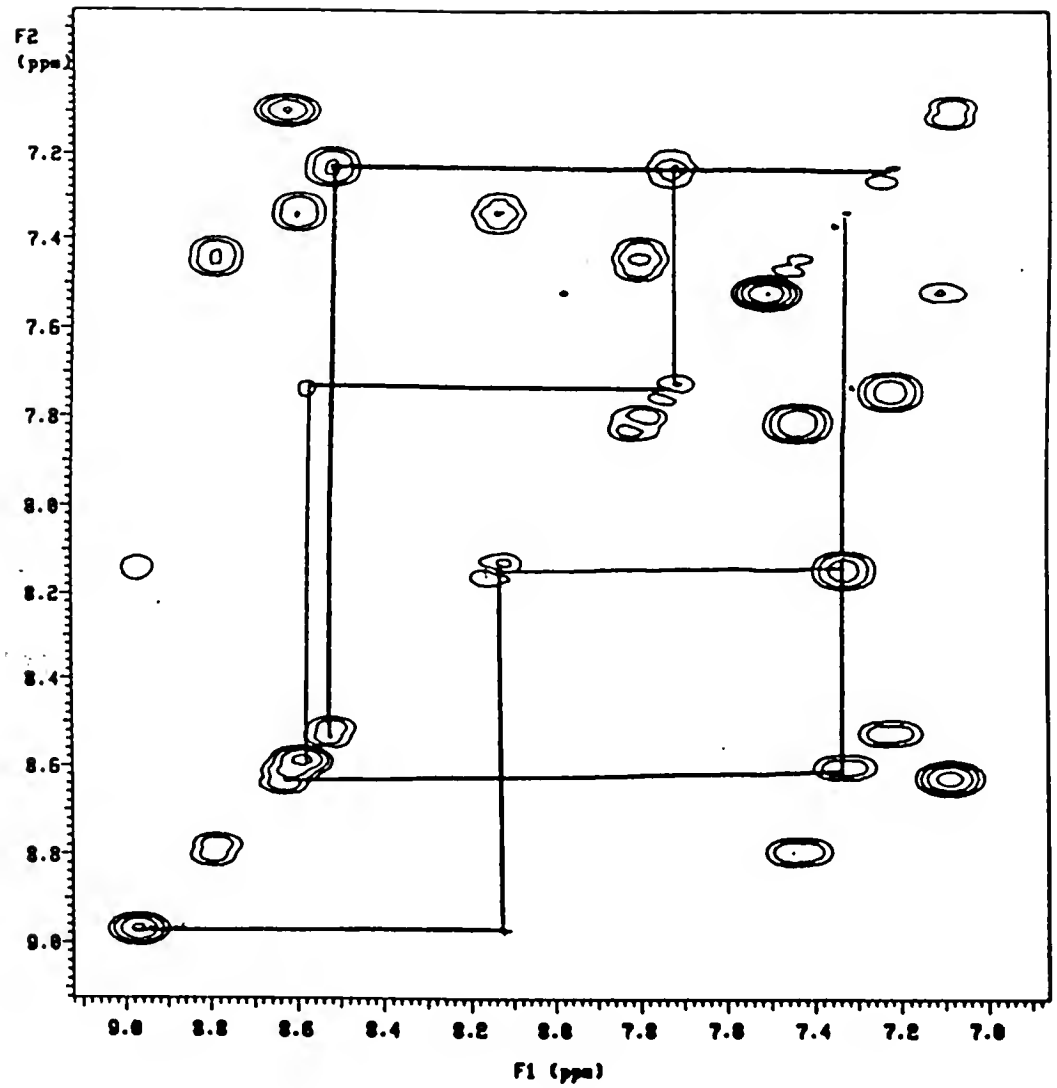


Figure 5-11

COSY at 300 MHz for nemertelline (5-3) in $CDCl_3$. The upper set of lines correlates the protons of the A ring and the lower set those of the D pyridyl ring.

α and γ signals for the low field 3-pyridyl ring must be associated with the D ring, i.e., they are due to protons 2′′′ and 4′′′. Because they are located across the ring from the lone electron pair of the nitrogen atom of the C ring they experience the deshielding effect of this electron pair causing them to be shifted to such low field.

This pair of low field signals was assigned by the early workers to 2 and 4 positions of the A ring[41] and not to the D ring as we have done. The crucial error giving rise to an incorrect structure in which the nitrogen atom of the C ring is positioned as in 5-1 and not 5-3.

Proton NMR Spectra of 5-1: The 300 MHz NMR spectrum of 5-1 in $CDCl_3$ is shown in Figure 5-12 along with shift assignments. Of the 14 aromatic proton signals, only three overlap seriously.

As before, the peak assignments were made using COSY (Figure 5-13), NOE difference, and splitting patterns. Splitting patterns are essential in identifying the degree and position of substitution in each ring.

Comparison of Proton NMR Spectra of 5-1 and 5-3: Table 5-1 shows the chemical shifts of 5-1 and nemertelline (5-3) in $CDCl_3$. Only the A ring protons have similar shifts. Five protons have shift differences of at least 0.3 ppm. Three of these (4′, 2′′′ and 4′′′) are associated with the presence or absence of the interannular nitrogen deshielding effect.

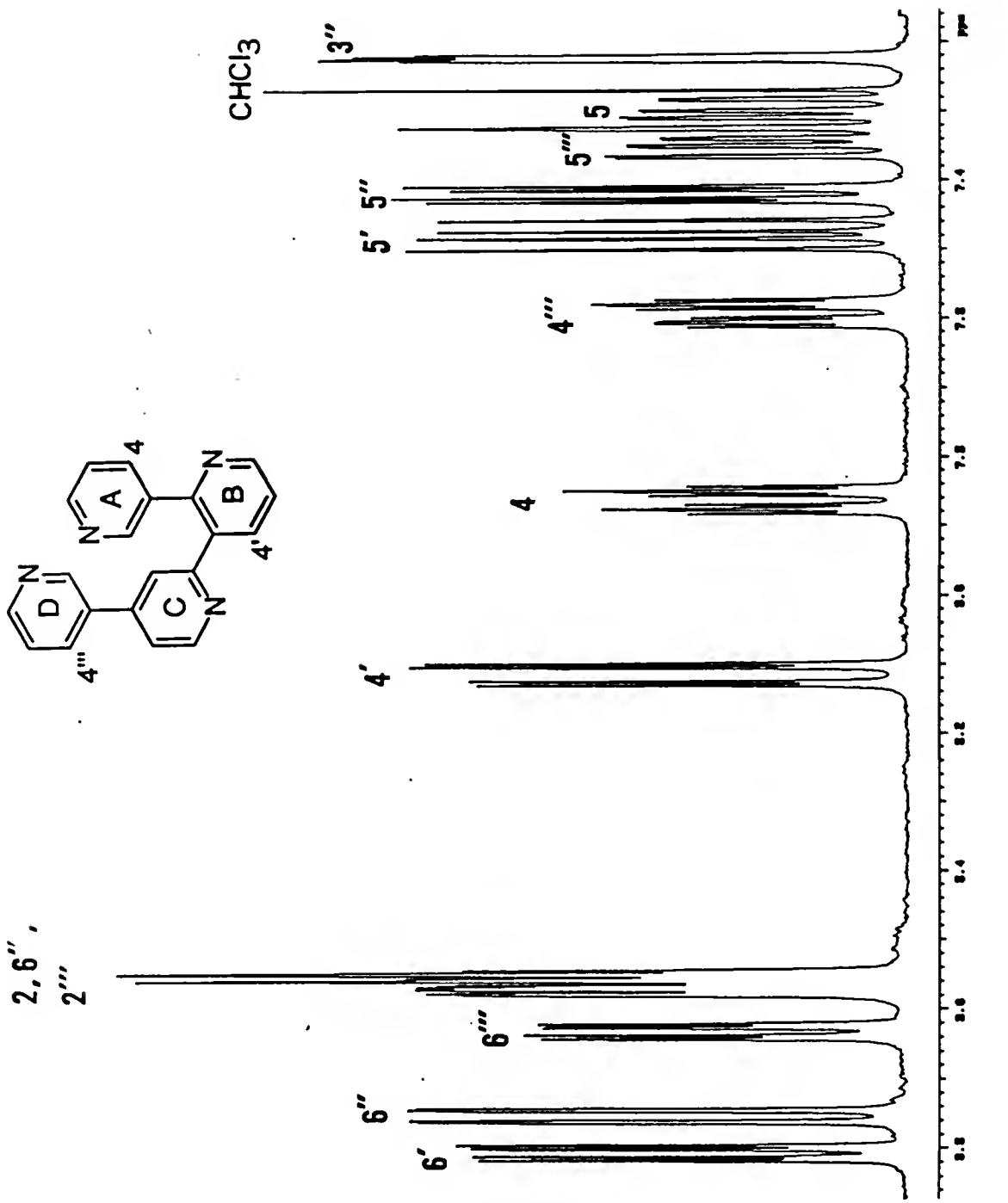


Figure 5-12 Proton NMR spectrum (300 MHz) of 5-1 in $CDCl_3$.

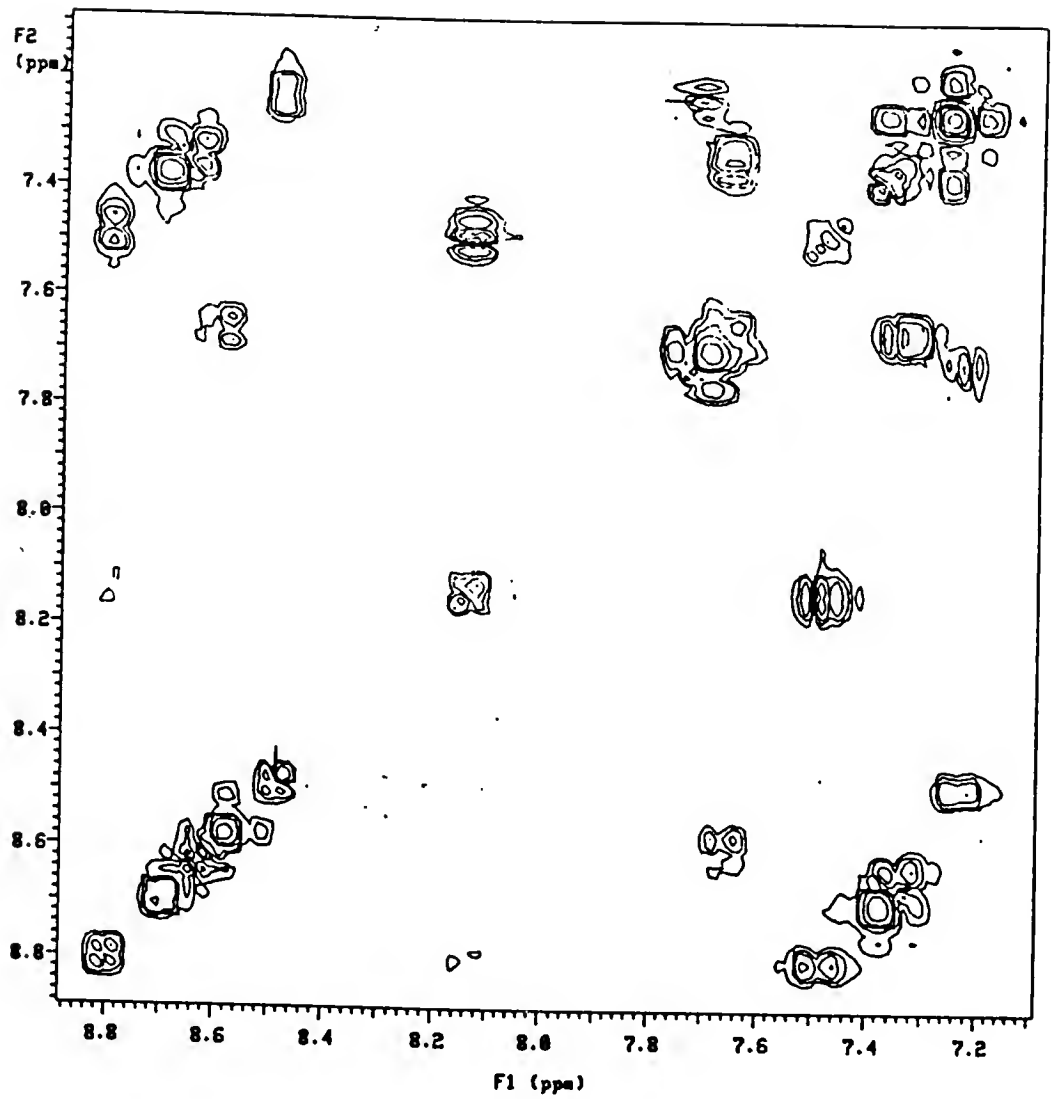


Figure 5-13

COSY at 300 MHz for 5-1 in $CDCl_3$.

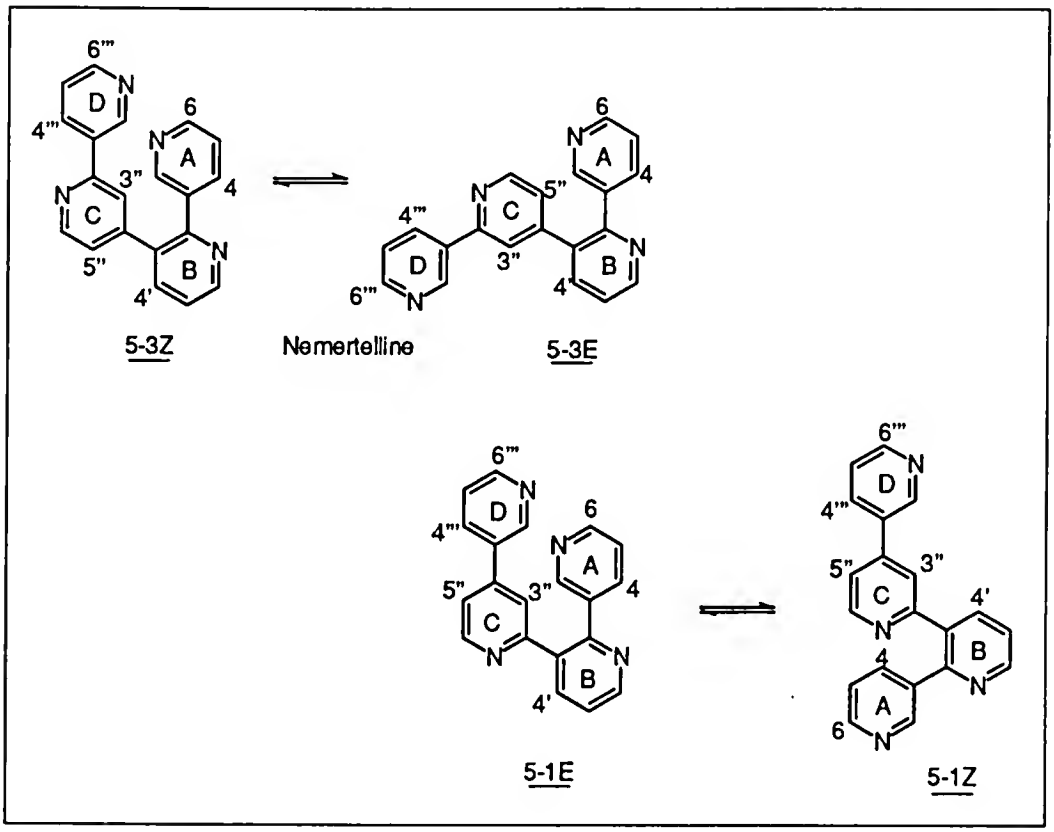
The reason for the large differences in the shifts for the other two protons, the 3'' and 5'' protons of the C ring, is less obvious and more subtle. The major conformation about the bond between the B and C rings is not the same for both isomers. That shown in 5-1 or 5-1E is correct. However, for 5-3 it is not 5-3Z, the conformation found in the solid state.[129] Rather it is conformation 5-3E that is present in chloroform. Hence, the position of protons 3'' and 5'' differ with respect to the shielding region of the A ring. In 5-1E, 3'' is located over the aromatic A ring and is shielded and in 5-3E, 5'' is shielded by the A ring.

Table 5-1. Chemical Shifts in ppm of 5-1 and 5-3 in $CDCl_3$

Cpd	A-Ring	B-Ring	C-Ring	D-Ring
5-1	8.57 (H2) 7.87 (H4) 7.30 (H5) 8.57 (H6)	8.12 (H4') 7.48 (H5') 8.82 (H6')	7.23 (H3'') 7.43 (H5'') 8.76 (H6'')	8.57(H2''') 7.61(H4''') 7.35(H5''') 8.64(H6''')
5-3	8.63 (H2) 7.77 (H4) 7.26 (H5) 8.56 (H6)	7.84 (H4') 7.49 (H5') 8.83 (H6')	7.55 (H3'') 7.13 (H5'') 8.67 (H6'')	9.01(H2''') 8.19(H4''') 7.38(H5''') 8.65(H6''')

We believe the incorrect structural assignment in 1976 is the result of assuming the wrong conformation for the natural product, shown then as 5-1Z, where the B and C rings have the Z conformation and not the E conformation as in our 5-1E arrangement. In the 5-1Z geometry the 2 and 4 protons of the A ring would be deshielded by the lone electron pairs on the

nitrogen atoms of the B and C rings, thus giving rise to the reported structural assignment. This small error marred the successful outcome of an otherwise difficult structure determination.



CHAPTER 6
THE CORRECT STRUCTURE OF THE OXIDIZED DIMER FORMED FROM 2,2′-BIPYRIDINE IN THE PRESENCE OF LITHIUM DIISOPROPYLAMIDE IS 2,2′:3′,2′′:6′′,2′′′-QUATERPYRIDINE.

Introduction

Lithium diisopropylamide (LDA) is known to react with pyridine to give a radical anion which then undergoes coupling to yield 4,4′-bipyridine and 2,4′-bipyridine in varying amounts depending on reaction conditions.[130] Recently, symmetrical bipyridines have been dimerized in the presence of LDA to give quaterpyridines. The mechanism is, again, believed to involve electron transfer and the formation of a reactive radical anion that gives rise to a quaterpyridine product following coupling and oxidation. Thus, LDA with 3,3′-bipyridine gives 3,3′:4′,4′′:3′′,3′′′-quaterpyridine by coupling at the 4-position[38] and 4,4′-bipyridine yields 4,4′:2′,2′′:4′′,4′′′-quaterpyridine on reaction at the 2-position.[131]

Recently, such an oxidative dimerization reaction has been reported for 2,2′-bipyridine in the presence of LDA and the product is said to be 6-1, 2,2′:4′,2′′:6′′,2′′′-quaterpyridine. The oxidized dimer was initially claimed to be the result of an unexpected, unsymmetrical coupling at the 4 and 6 positions of two bipyridines.[42] Recently, the original

author has corrected the structure with the help of X-ray analysis and it is now claimed to be 6-2, 2,2′:3′,2′′:6′′,2′′′-quaterpyridine.[132]

We have independently prepared authentic 6-1 by a simple synthesis utilizing a palladium(0)-catalyzed cross-coupling reaction and have found that the proton NMR spectrum of our quaterpyridine unmistakably does not match that of the product of the reaction with LDA.

We have repeated the LDA induced coupling reaction of 2,2′-bipyridine and have obtained the reported product in comparable yield. By proton NMR analysis, we show this material to be the corrected structure 6-2, 2,2′:3′,2′′:6′′,2′′′-quaterpyridine,[132] a substance having been formed by coupling at the 3 and 6 positions of two bipyridine rings not the 4 and 6 positions as formerly claimed. The dihydro precursor of 6-2 also has been identified.

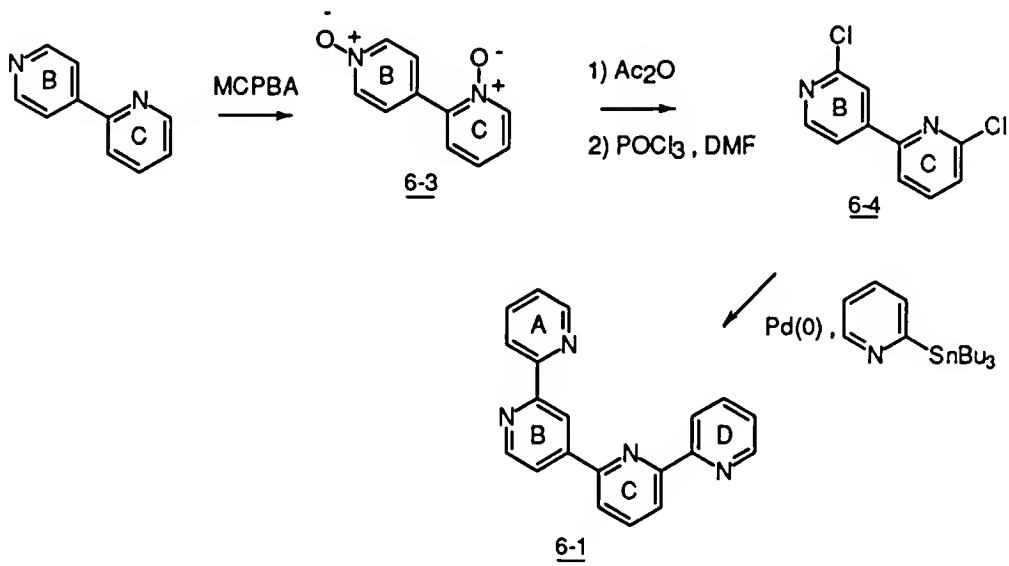
Results and Discussion

Independent Synthesis of 2,2′:4′,2′′:6′′,2′′′-Quaterpyridine (6-1)

Employing strategies we recently developed for the construction of unsymmetrical quaterpyridines,[132,133] the synthesis of 6-1 was straightforward starting with commercially available 2,4′-bipyridine (Figure 6-1). This bipyridine, which contains the B and C rings of the

quaterpyridine, was di-N-oxidized with MCPBA to give 6-3 (54%). The N-oxide synthons allow the further functionalization of the bipyridine rings into 2′,6-dichloride 6-4. It was advantageous to first convert 6-3 into the dipyridone with acetic anhydride and then to make dichloride 6-4 with $POCl_3$/DMF and thereby minimize the formation of isomers.[99] Direct conversion of 6-3 into dichloride 6-4 with $POCl_3$/DMF was unsatisfactory because it yielded a 1:1 mixture of 6-4 and 2′,4-dichloride 6-5.

Figure 6-1



Since both isomers representing chlorination at the 4 and 6 positions of the 2-pyridyl ring were at hand, identification of each one was quite easy. The desired 6-chloro compound 6-4 showed a characteristic triplet for H-4 partially overlapped by H-5′ at δ 7.8 ($CDCl_3$). Addition of both A rings by

palladium-catalyzed cross-coupling with 2-(tributylstannyl) pyridine[79] completed the synthesis of 6-1 (57%).

The proton NMR spectrum of 6-1 along with its chemical shift assignments is given in Figure 6-2. They are based on COSY (Figure 6-3) and NOE difference spectra.

Proof of the Structure of 6-2, the Quaterpyridine Formed in the Presence of LDA

The proton NMR spectrum of 6-2 is given in Figure 6-4. A comparison with our spectrum of 6-1 clearly indicates the two quaterpyridines are not the same material. They both must have an unsymmetrical four ring A-B-C-A and not a symmetrical A-B-B-A structure, owing to the large number of signals. Because there are just six different ways to join two 2,2′-bipyridines together to give such an unsymmetrical material, Table 1, and one of these, entry 4, is our newly synthesized material 6-1, there are just five possibilities for the product of the LDA reaction. Of these five structures all but the material in question have not yet been prepared.

With both 6-1 and 6-2 the A ring protons are easily assigned by their similarity to the chemical shifts and spin coupling constants of 2,2′-bipyridine itself. The key to the identification of the structure of 6-2 is the substitution pattern of the B and C rings. The COSY spectrum (Figure 6-5) unambiguously establishes that the three well separated protons at δ 8.79, 8.14, and 7.48 are contiguous and therefore

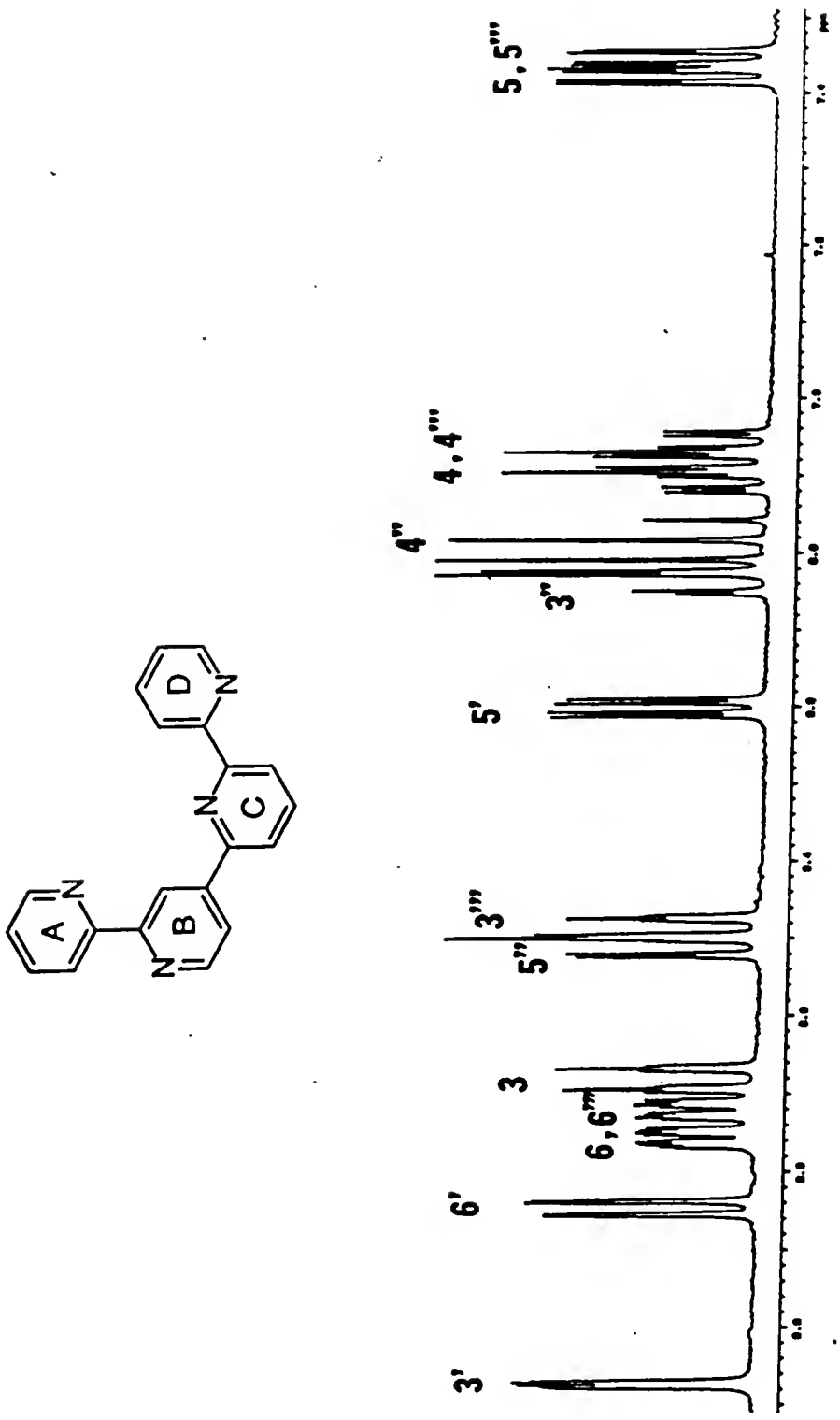


Figure 6-2. Proton NMR spectrum of quaterpyridine 6-1 in $CDCl_3$.

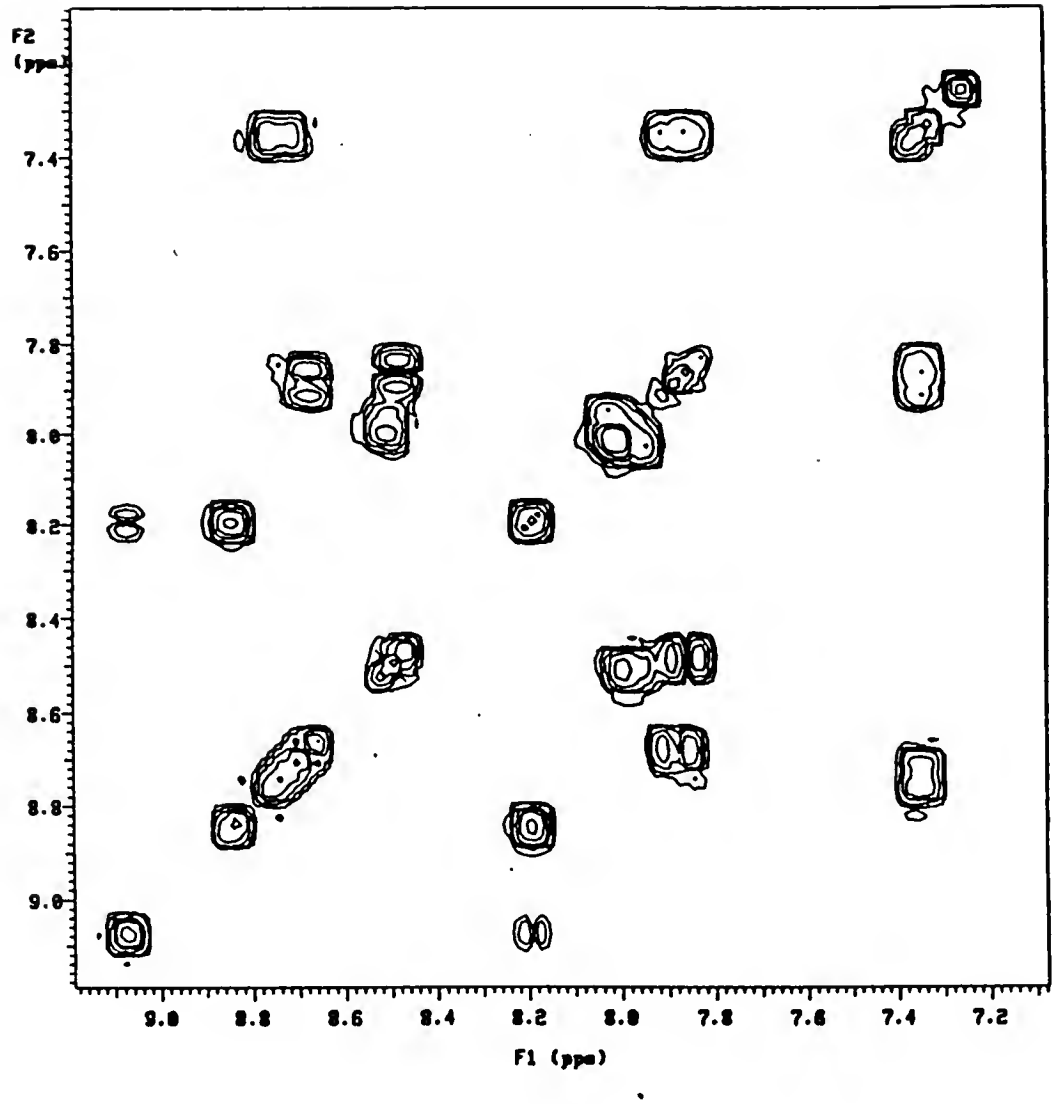


Figure 6-3. COSY spectrum of quaterpyridine 6-1 in $CDCl_3$.

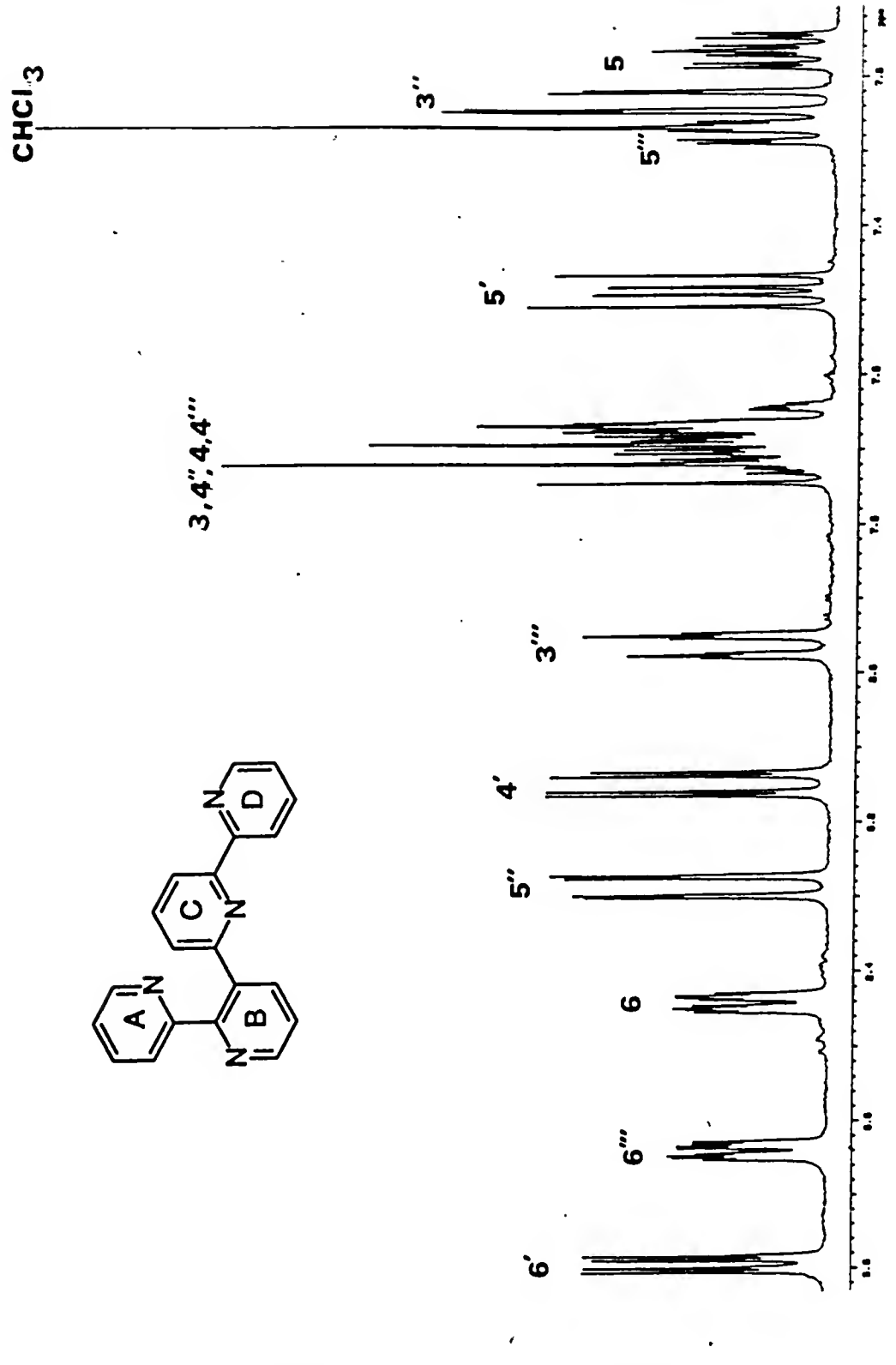


Figure 6-4. Proton NMR spectrum of quaterpyridine 6-2 in $CDCl_3$.

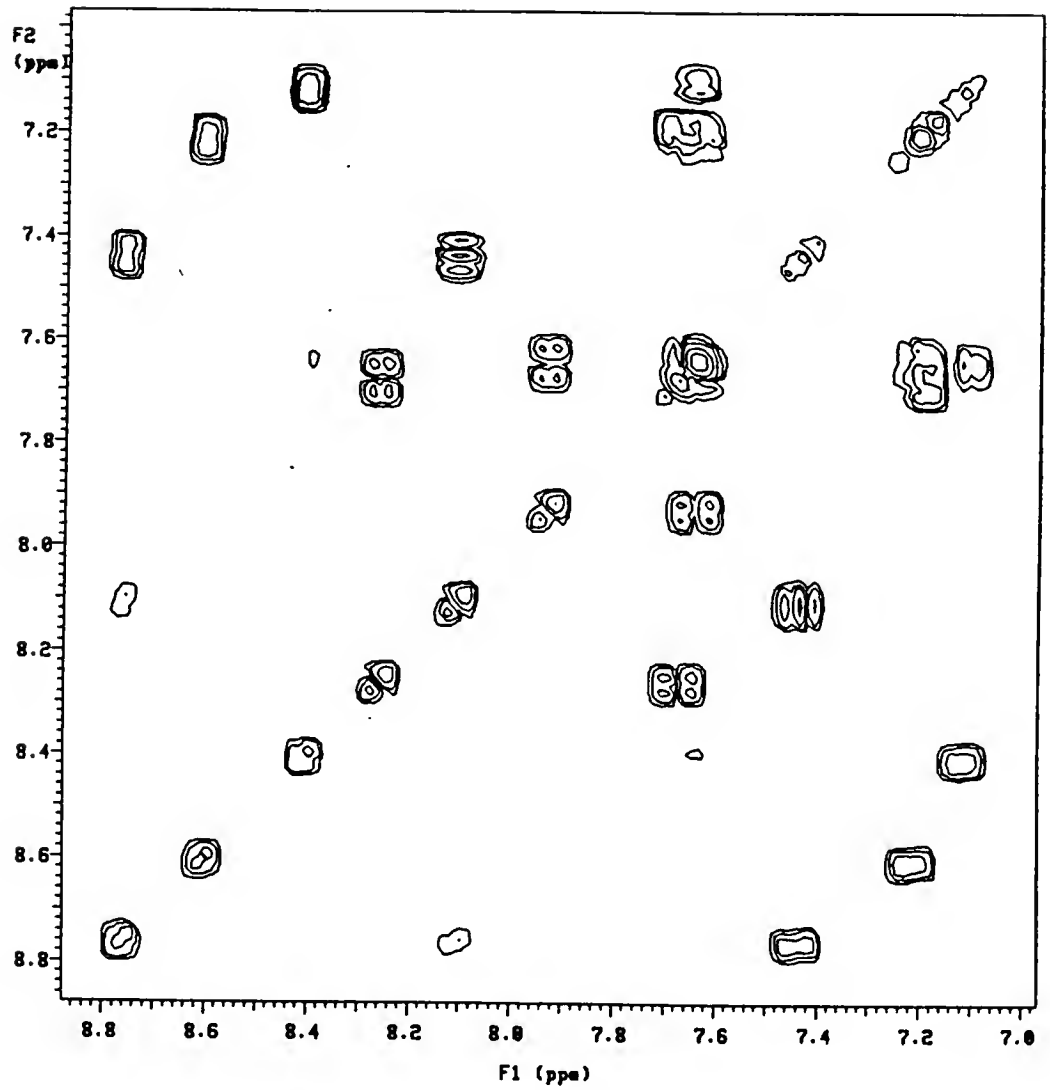


Figure 6-5

COSY spectrum of quaterpyridine 6-2 in $CDCl_3$.

belong to one of these rings. Importantly, their major coupling constants of 5 and 9 Hz unequivocally require them to be part of a 2,3-disubstituted ring and not, as originally suggested, part of a 2,6-disubstitued pyridine where both *ortho* couplings to a proton in position 4 would have essentially the same value.[39] Typically, for a pyridine or a bipyridine the coupling constant for the 2,3-position is smaller (5 Hz) than that for the 3,4-position (8 Hz).[134] Thus, the B ring is 2,3-disubstituted and only the first three entries in Table 1 represent correct possible structures.

Table 6-1. Six Possible Ways of Joining Together Two 2,2′-BPYs to Form Unsymmetrical QPYs of the Type A-B-C-A.

Entry	B Rxn Site	C Rxn Site	QTPY Product
1	3′	2′′	A-$B_{3'}$-$C_{2''}$-A
2	3′	3′′	A-$B_{3'}$-$C_{3''}$-A
3	3′	4′′	A-$B_{3'}$-$C_{4''}$-A
4	4′	2′′	A-$B_{4'}$-$C_{2''}$-A
5	4′	3′′	A-$B_{4'}$-$C_{3''}$-A
6	5′	2′′	A-$B_{5'}$-$C_{2''}$-A

The incorrect assignment of these three signals to a 2,6-disubstituted C ring probably was the crucial error in the original report.

Unfortunately, the overlap of four protons at δ 7.65 makes the identification of the C ring more difficult. However, an NOE difference spectrum was most revealing.

Irradiation of the signal at δ 8.28 (H5'') caused this four proton multiplet to reduce to a simple one proton triplet with a 7.5 Hz coupling constant, showing that this resonance must be associated with the proton at position 4'' of the C ring (Figure 6-6). Therefore, this ring must be 2,6-disubstituted as in our C ring of 6-2 and not 2,4-disubstituted as in the B ring of 6-1. Thus, the correct structure of the LDA reaction product must be that given in 6-2, entry 1, Table 1. The complete signal assignment is found in the experimental section.

The partial proton spectrum of a crude dihydro precursor of 6-2 isolated prior to its oxidation is given in Figure 6-7. The spectrum is consistent with the C ring being either a 1,2-dihydro-2,6 or a 1,4-dihydro-2,4 disubstituted pyridine with its characteristic coupling constants for double (9 Hz) and single bonds (6 Hz) as well as allylic coupling (5 Hz).[135] Two of the four carbon bound protons have an eight line coupling pattern characteristic of a four spin system while the one at the highest field has 16 lines consistent with an additional coupling to the proton on nitrogen. We suggest this material is 6-6 (Figure 6-8), having a nucleophilic carbon bonded to the 2'' position of the C ring.

Mechanism of Coupling with LDA

We speculate that the coupling process proceeds by an ionic mechanism in which 3-lithiated BPY 6-7 adds to the 6

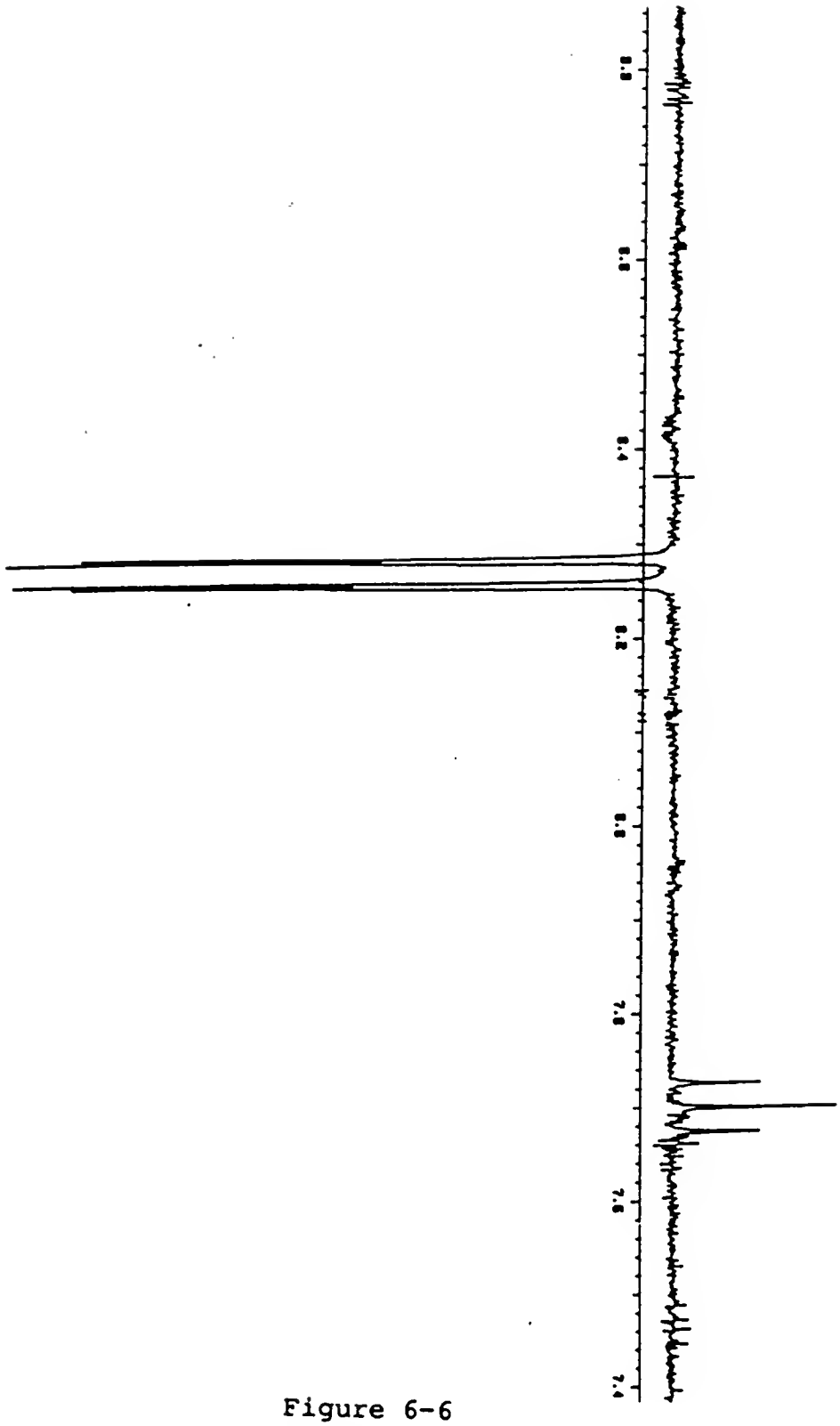


Figure 6-6

NOE difference spectrum of quaterpyridine 6-2 in $CDCl_3$ with irradiation of H5'' at 8.28 ppm.

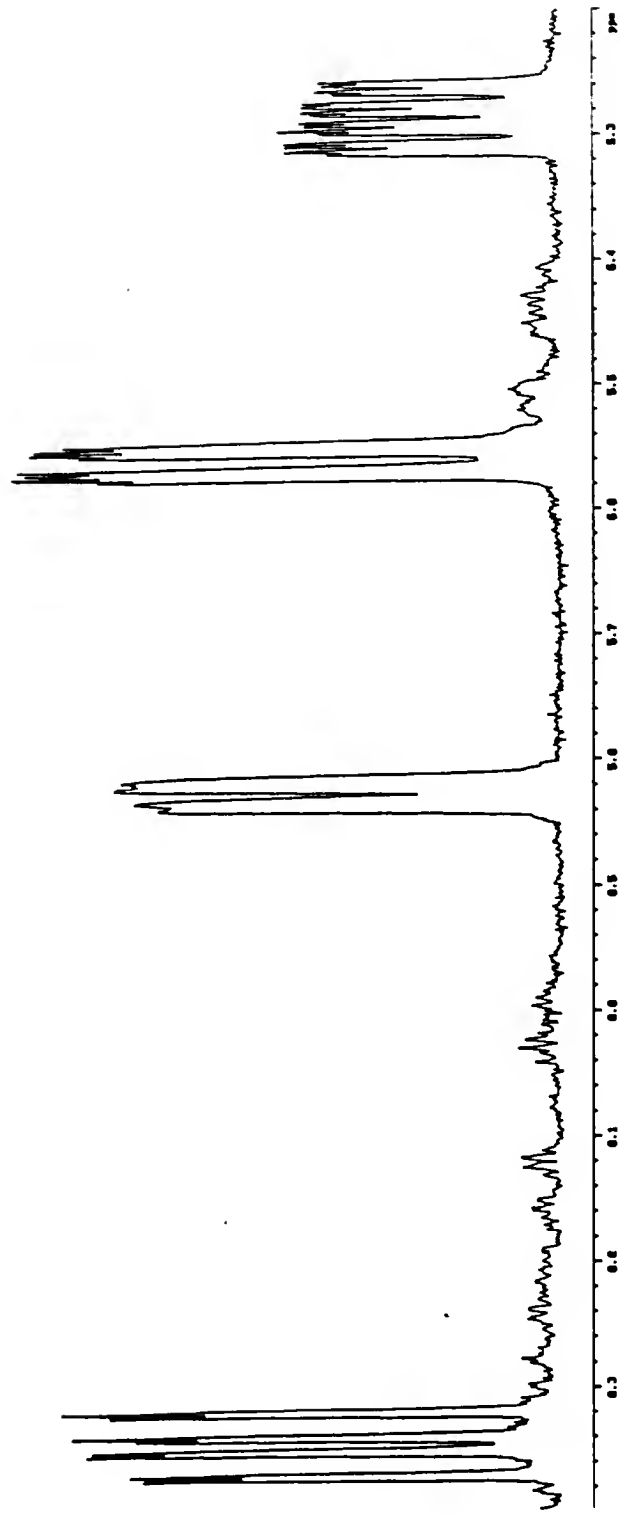
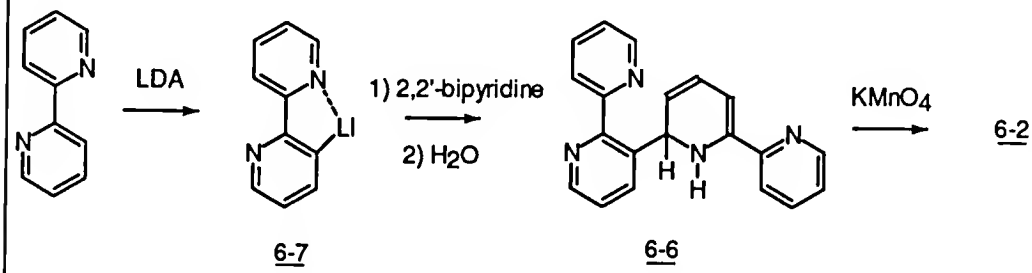


Figure 6-6. Partial proton NMR spectrum of the upfield portion of 6-6, the dihydro precursor of QTPY 6-2 in $CDCl_3$.

position of a second bipyridine ring to give the observed dihydro intermediate 6-6 following quenching with a proton source. Oxidation then gives the quaterpyridine product. Carbon nucleophiles are known to add to the 6 position of 2,2′-bipyridine.[119,136]

Figure 6-8



Supporting this suggestion is the rich *ionic* chemistry associated with deprotonation and lithiation by LDA of ring positions of a wide variety of aromatic nitrogen heterocycles.[117,137] But our attempts to find evidence for the proposed 3-lithiated 6-7 by quenching the LDA reaction mixture with either D_2O or CH_3OD and then examinining by NMR the recovered BPY for evidence of deuterium incorporation were unsuccessful. Curiously, the 3 position of the ruthenium complex of 2,2′-bipyridine is known to undergo hydrogen-deuterium exchange but only with CD_3OD-CD_3ONa-DMSO and exclusively at the 3 and 3′ sites of the bipyridine in the metal complex.[138]

CHAPTER 7
STRATEGIES FOR THE SYNTHESIS OF UNSYMMETRICAL QUATERPYRIDINES USING PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

Introduction

Unsymmetrical and unsubstituted quaterpyridines of the type A-B-C-D where the letters represent individual pyridine rings are largely unknown substances. Of the 426 theoretically possible structures, just seven were reported prior to the start of our investigations. Many contain the 2,2′-bipyridine unit because of the interesting ability of this bipyridine to coordinate various metal ions.[139] Five are symmetrical structures of the type A-B-B-A; they are easily prepared by homocoupling the A-B portions under a variety of conditions.[36-40] Of the two reported unsymmetrical quaterpyridines, both were originally assigned incorrect structures. Both structures[41,42] have been corrected by either an independent synthesis based on palladium(0)-catalyzed cross-coupling chemistry or X-ray analysis.[129,132]

We now demonstrate a strategy that has considerable generality for the synthesis of unsymmetrical quaterpyridines of the types A-B-C-D and A-B-C-A. Individual pyridine rings are joined together in the presence of a Pd(0) catalyst using a pyridyl halide and an organometallic reagent such as a

pyridyl stannane (Stille coupling[2]) or a borane (Suzuki coupling[70]). Of the six different possible arrangements for the two central bipyridine rings, we start with two different model bipyridines that comprise the central B-C portion, one linked 2,4′ and the other 2,3′ and show how to functionalize selectively one pyridine ring at a time in order to achieve selective cross-coupling. Liberal use is made of a pyridine N-oxide synthon and its specific conversion into an α-chloro pyridine suitable for the metal-catalyzed cross-coupling. In one instance the N-oxide atom was introduced onto the preformed bipyridine by controlled N-oxidation while in another example a stannylated pyridine N-oxide directly gave N-oxidized bipyridine on cross-coupling with a chloropyridine.

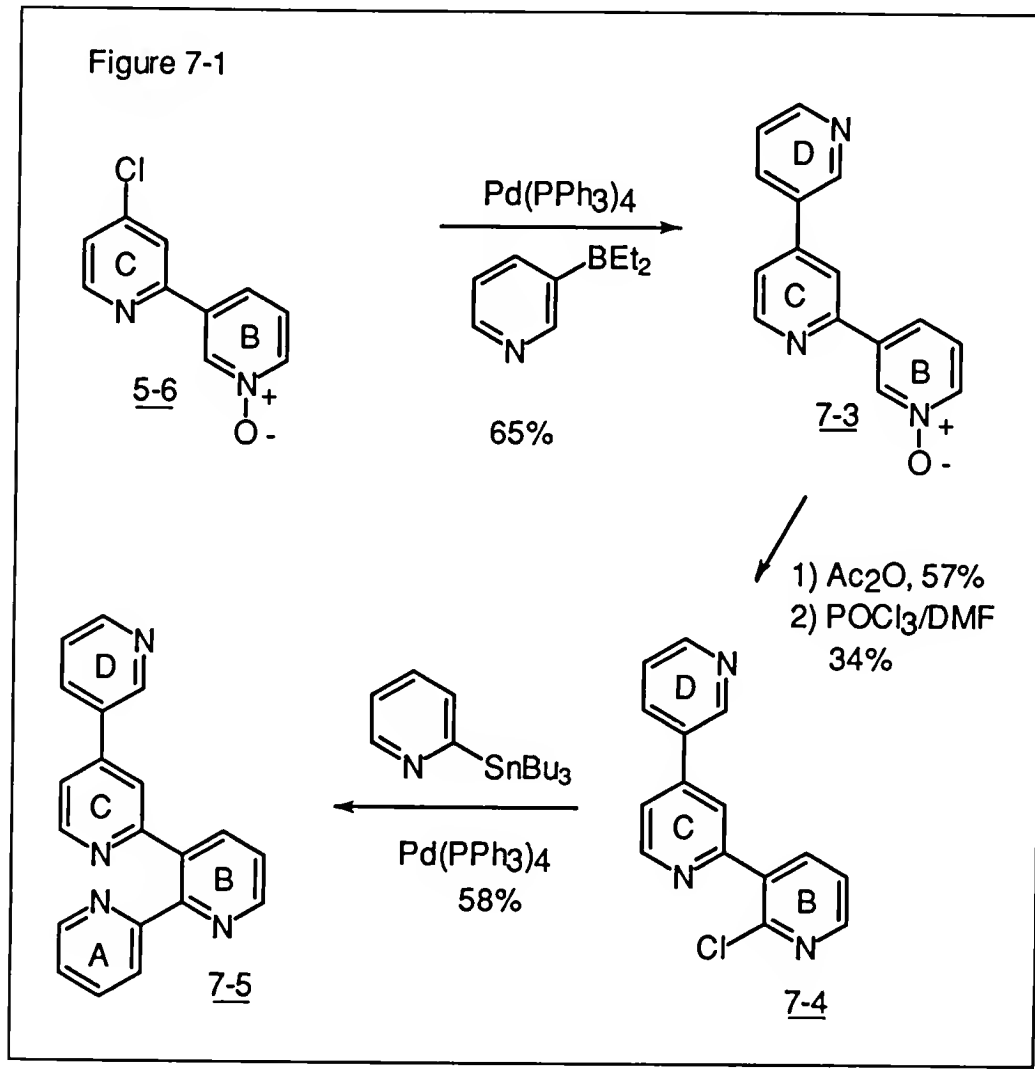
Results and Discussion

The A-B-C-D Geometry of 2,2′:3′,2′′:4′′,3′′′-Quaterpyridine (7-5)

The known B-C precursor, 4-chloro-2,3′-bipyridine-1′-oxide[132] (5-6) in Figure 7-1, was made from 2,4-dichloropyridine and diethyl(3-pyridyl)borane by Pd(0) coupling followed by regioselective N-oxidation at the sterically less hindered nitrogen atom. To this was added the D-ring in the form of diethyl(3-pyridyl)borane in the presence of Pd(0) to yield terpyridine 7-3. The presence of the N-oxide group in 7-3 allowed the specific conversion of the B-ring to

chloride 7-4. It was advantageous to carry out this conversion in a two-step rather than a one-step sequence, first making with acetic anhydride the pyridone and then converting it into the chloride with $POCl_3$/DMF. With the two-step approach the more sterically hindered α position was specifically functionalized. Direct conversion of the N-oxide with $POCl_3$ and DMF was not attempted because often a mixture of both the α and γ chlorinated products is produced.[99]

Figure 7-1



Proof that the conversion of the N-oxide 7-3 to the more hindered α-chloride actually took place to give terpyridine 7-4 was easily demonstrated by the coupling pattern of the B-ring which contained three highly coupled protons and not just two as would have resulted from the undesired α′ or γ chloro isomers. Eight of the ten different proton signals in 7-4 ($CDCl_3$) are clearly resolved making their assignment quite easy. Addition of the A-ring by means of 2-(tributylstannyl) pyridine[79] with Pd(0) completed the synthesis to give 7-5.

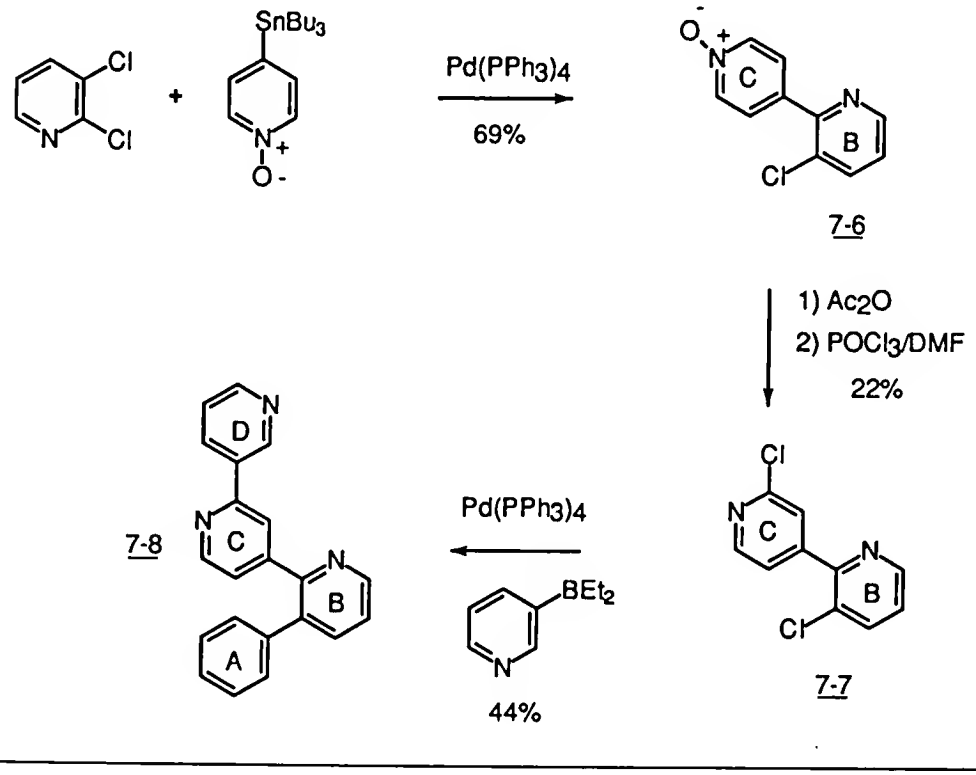
Clearly in our synthesis the bonding site of the A and D pyridyl rings easily could have been varied by using an isomerically metallated pyridine starting material. In this way and by keeping the same bonding pattern of the original B and C rings a total of nine quaterpyridines could easily have been prepared.

The A-B-C-A Geometry of 3,3′:2′,4′′:2′′,3′′′-Quaterpyridine (7-8)

3-Chloro-2,4′-bipyridine-1′-oxide (7-6) in Figure 7-2 was easily prepared from 2,3-dichloropyridine and 4-(tributylstannyl)pyridine N-oxide[113] by the palladium route discussed in chapter 3. We assume that coupling took place at the 2 and not the 3 position as expected from a consideration of the mechanism of oxidative addition of palladium which usually takes place at the site more easily undergoing nucleophilic attack.[46,140,141] Again, the N-oxide was converted to

the α chloro derivative by the two-step acetic anhydride-$POCl_3$ method to give dichloride 7-7 which then with diethyl(3-pyridyl)borane and Pd(0) gave the quaterpyridine 7-8 having the same two 3-pyridyl terminal rings. Others have used a similar approach first making the B-B portion followed by coupling to form an A-B-B-A quaterpyridine having methyl groups.[142] Had our assumption been wrong about the site of coupling in the first cross-coupling step to prepare 7-6 in Scheme 2, the final product would have been an isomeric quaterpyridine natural product, nemertelline, that we have independently prepared by a convergent synthesis.[129]

Figure 7-2



Clearly, chloro N-oxide 7-6 could have been cross-coupled to some other pyridine ring and then the N-oxide of the resultant terpyridine could have been converted to a new chloride as we have done. This new terpyridine, in turn, could have been cross-coupled to a different fourth ring to give a family of nine isomeric quaterpyridines of the A-B-C-D type.

Chemical shift assignments for the quaterpyridines are found in the Experimental Section and are based on COSY and NOE difference spectra of samples in $CDCl_3$. Because there is less signal overlap for these compounds when dissolved in CD_3OD, it is useful to record spectra with both solvents.

Overview of Quaterpyridine Preparations

All three isomers of the potential stannyl pyridine[79] starting materials are known as well as the three corresponding boranes.[44] However, the 2-pyridyl borane has never been cross-coupled in a reaction with Pd because it forms an unusually stable cyclic dimer resembling a dihydroanthracene.[143] The 3- and 4-stannylated pyridine N-oxides are easily prepared but the 2 isomer is still unknown.[113]

A large number of mono and dihalogenated pyridines are commercially available for the preparation of bipyridines by coupling routes. Still other dihalides may now be prepared by direct lithiation of a suitably activated pyridine with LDA followed by halogenation of this lithiated material.[117,137]

Cross-couplings of dihalopyridines may be made to be selective by the choice of the halogen where the reactivity order is I > Br > Cl and by the realization that the α and γ positions are more reactive than a β position when the halides are the same. Thus, considerable control in the preparation of the crucial central bipyridines is possible.

CHAPTER 8
EXPERIMENTAL

Diethyl(3-pyridyl)borane, 4-chloropyridine-N-oxide, 3-amino-2-chloropyridine, tributyltin chloride, phosphorus oxychloride, 2,3-dichloropyridine, 2.5 M n-BuLi, 2-bromopyridine, 57-80% m-chloroperbenzoic acid (MCPBA), 2,2′-bipyridine, 2,4′-bipyridine, 1.5 M lithium diisopropylamide, acetic anhydride, 4-nitrophenethyl bromide, urea-H_2O_2 complex, methyl triflate, methyl iodide, methyl tosylate, 4-nitropyridine-n-oxide, 6-chloronicotinamide, 4-bromopyridine, 4-chloropyridine, 3-iodopyridine, 5-bromopyrimidine, chloropyrazine, 3-bromoquinoline, 4-bromoisoquinoline, tetrakis(triphenylphosphine) palladium(0), tris-dibenzylideneacetone palladium dimer, 1,2-(diphenylphosphino)ethane palladiun(II) dichloride were purchased from Aldrich Chemical Company or Acrõs Chemical Company. 3-(Tributylstannyl)pyridine[79], 2-(tributylstannyl) pyridine[79], 4-(tributylstannyl)pyridine[79], 3-(tributylstannyl) quinoline[79], and 4-(tributylstannyl)isoquinoline[79] were prepared by literature methods from tri-n-butylstannyl chloride and the corresponding brominated pyridine, quinoline, or isoquinoline via their Grignard or lithium reagents.

Quaternized hetaryl iodides were prepared with neat methyl iodide unless indicated otherwise. Quaternized hetaryl tosylates were prepared in chloroform or ethyl acetate unless indicated otherwise. No attempt was made to optimize the yields of the final cross-coupled products; all yields refer to isolated materials. Variable amounts of water were found on repeated combustion analysis of N-oxides; the amount of water found in the solid seems to be dependent on the method and extent of drying. Reverse phase octadecylated silica gel was purchased from Aldrich. Flash chromatography made use of Kieselgel 60 230-400 mesh or alumina 80-200 mesh. Thin layer chromatography used Whatman polyester backed silica gel plates. ^{1}H NMR spectra were recorded on Varian Gemini 300 (300 MHz), QE 300 (300 MHz), or a Varian Unity 500 (500 MHz). Grignard reactions were initiated with I_2 or 1,2-dibromoethane. Solvents often were freshly distilled and degassed by bubbling N_2 through them for 15-30 minutes. All melting points are uncorrected. The drying agent was either sodium or magnesium sulfate.

5-Chloro-3,3'-bipyridine-1-oxide (2-1): A mixture of 3,5-dichloropyridine-N-oxide[55] (400 mg, 2.44 mmol), diethyl(3-pyridyl)borane (0.36 g, 2.4 mmol) and tetrakis-(triphenylphosphine)palladium(0) (0.30 mg, 0.25 mmol) in 20 mL of degassed THF was allowed to stir at room temperature for 5 min under N_2. After the addition of potassium carbonate (0.66 g, 4.8 mmol) in 10 mL of water, the mixture was heated at

reflux while stirring. After 12 h, the reaction was allowed to cool and then was diluted with 30 mL of EtOAc and 30 mL of water. The layers were separated and the aqueous layer was concentrated to give a solid consisting of product and buffer which was extracted three times by shaking with 20 mL of MeOH. The MeOH washes were combined and concentrated in the presence of 20 g of silica gel. Flash chromotography using 70/30 EtOAc/MeOH gave 350 mg of an off-white solid which was recrystallized with EtOAc and isopropyl alcohol to yield 300 mg (1.40 mmol) of a white solid (60% yield, mp 168-170 °C). ^{1}H NMR (DMSO-d_6): δ 8.98 (H2′, 1H, d, J = 2 Hz), 8.70 (H6, 1H, s), 8.65 (H6′, 1H, dd, J = 2 and 5 Hz), 8.56 (H2, 1H, s), 8.20 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 7.94 (H4, 1H, s), 7.53 (H5′, 1H, dd, J = 5 and 9 Hz). The compound was dried under vacuum at 100 °C and repeated analyses gave results indicating the presence of variable amounts of water (0.25 and 0.5 equivalents). Anal. Calcd for $C_{10}H_7N_2OCl$. $0.5H_2O$: C, 55.70; H, 3.74; N, 12.99. Found: C, 55.63; H, 3.54; N, 12.73.

3,3′:5′,3′′-Terpyridine-1′-oxide (2-2) and Trihydrochloride: A mixture of 3,5-dichloropyridine-N-oxide[55] (0.200 g, 1.22 mmol), diethyl(3-pyridyl)borane (0.360 g, 2.44 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 20 mL of degassed THF was allowed to stir at room temperature for 5 min under N_2. Following the addition of potassium carbonate (0.505 g, 3.65 mmol) in 10 mL of water, the reaction was heated at reflux while stirring. After 12 h,

the reaction was allowed to cool then was diluted with 30 mL of EtOAc and water. The aqueous layer was separated and concentrated. The resultant white solid was extracted three times with 20 mL of MeOH to remove product from buffer. The MeOH washes were combined and concentrated onto 20 g of silica gel. Flash chromotography using an eluant of 70/30 EtOAc/MeOH gave 190 mg (0.76 mmol) of an off-white solid which was recrystallized with EtOAc and isopropyl alcohol to yield 150 mg (0.602 mmol) of a white solid (50% yield, mp > 220 °C). ^{1}H NMR (DMSO-d_6): δ 8.98 (H2′, 2H, d, J = 2 Hz), 8.70 (H2 and H6, 2H, s), 8.65 (H6′, 2H, dd, J = 2 and 5 Hz), 8.10 (H4′, 2H, dt, J = 2, 2 and 9 Hz), 7.94 (H4, 1H ,s), 7.53 (H5′, 2H, dd, J = 5 and 9 Hz). Anal. Calcd for $C_{15}H_{11}N_3O$. $0.75H_2O$: Found C, 68.77; H, 15.64; N, 4.30. Calcd C, 68.56; H, 15.99; N, 4.79. Addition of the product to ether-hydrogen chloride gave a precipitate, mp >220 °C. Anal. Calcd for $C_{15}H_{11}N_3O.3HCl$: C, 50.23; H, 3.93; N, 11.72. Found: C, 50.10; H, 3.53; N, 11.29.

3-Bromoquinoline-1-oxide (2-3): To a solution of 3-bromoquinoline (2.0 mL, 14.7 mmol) in chloroform (35 mL) was added 50 % m-chloroperoxybenzoic acid (7.6 g, 44 mmol). The solution was allowed to stir at room temperature overnight. The insoluble m-chlorobenzoic acid was filtered off and the filtrate was washed twice with satd. $NaHCO_3$. The $CHCl_3$ was dried and concentrated to a brown solid. A flash silica gel column using 80% hexanes/20% EtOAc gave 1.4 g (6.2 mmol) of an off-white solid (43% yield, mp 192-195 °C, lit[59] mp 194-196°C).

^{1}H NMR (DMSO-d_6): δ 8.85 (H2 or H4, 1H, s), 8.45 (H5 or H8, 1H, d, J = 9 Hz), 8.28 (H2 or H4, 1H, s), 8.04 (H5 or H8, 1H, d, J = 8 Hz), 7.80 (H6 and H7, 2H, m).

3-(3-Pyridyl)quinoline-1-oxide (2-4): A mixture of 3-bromoquinoline-1-oxide (1.2 g, 5.4 mmol), diethyl(3-pyridyl)borane (0.79 g, 5.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.25 mmol) in 30 mL of degassed tetrahydrofuran was stirred at room temperature for 5 min under N_2. Following the addition of sodium bicarbonate (2.3 g, 27 mmol) in 15 mL of water the reaction was heated at reflux while stirring. When starting material was consumed (TLC), after 36 h, the reaction was cooled to 0°C and the insoluble catalyst was filtered off. To the filtrate, water (30 mL) and EtOAc (30 mL) were added; after separation the water layer was concentrated to a brown solid. The material was triturated with 50 mL of methanol and the insolubles were filtered off. The methanol was concentrated in the presence of 20 g of silica gel. Column chromatography with an eluant of 85% EtOAc and 15% methanol gave 0.75 g (3.4 mmol) of an off-white solid (63% yield, mp 132-134 °C). ^{1}H NMR (DMSO-d_6): δ 9.07 (H2 and H2′, 2H, s), 8.65 (H6′, 1H, dd, J = 2 and 5 Hz), 8.53 (H5 or H8, 1H, d, J = 10 Hz), 8.38 (H4, 1H, s), 8.29 (H4′, 1H, dt, J = 2, 2 and 8), 8.14 (H5 or H8, 1H, d, J = 10 Hz), 7.81 (H6 and H7, 2H, m), 7.55 (1H, dd, J = 5 and 8 Hz). Anal. Calcd for $C_{14}H_{10}N_2O$. $0.25H_2O$: C, 74.15; H, 4.67; N, 12.35. Found: C, 73.77; H, 4.71; N, 12.11.

3-(2-Pyridyl)quinoline-1-oxide (2-5): A solution of 3-bromoquinoline-1-oxide (546 g, 2.44 mmol), 2-(tributylstannyl)pyridine (900 mg, 2.44 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.260 mmol) in 30 mL of degassed DMF was stirred at refux for 48 h under N_2. The reaction was cooled to 0 °C and the insoluble catalyst was removed by filtration. The filtrate was concentrated to a brown oil and purified by column chromatography with Kieselgel and 95/5 EtOAc/MeOH. The result was 300 mg of a slightly yellow solid which was triturated with 30 mL of hexanes to give 245 mg of slightly yellow solid (45% yield, mp 139-141 °C). ^{1}H NMR (DMSO-d_6): δ 9.25 (H2, 1H, s), 8.73 (H6′, 1H, d, J = 5 Hz), 8.67 (H4, 1H, s), 8.53 (H5 or H8, 1H, d, J = 10 Hz), 8.21 (H3′ and H5 or H8, 2H, m), 7.98 (H4′, 1H, dt, J = 2, 9 and 9 Hz), 7.82 (H6 and H7, 2H, m), 7.47 (H5′, 1H, dd, J = 5 and 9 Hz). Anal. Calcd for $C_{14}H_{10}N_2O$. $1.25H_2O$: C, 68.14; H, 5.11; N, 11.35. Found: C, 68.62; H, 4.77; N, 11.30.

1-Methyl-3-(3-pyridyl)quinolinium Iodide (2-7): A mixture of 3-bromo-1-methylquinolinium iodide[64] (1.3 g, 3.7 mmol), diethyl(3-pyridyl)borane (0.55 g, 3.7 mmol) and 1,2-(diphenylphosphino)ethane palladium(II) dichloride (0.20 g, 0.37 mmol) in 30 mL of degassed THF was allowed to stir at room temperature for 5 min under N_2. To this was added sodium bicarbonate (1.6 g, 19 mmol) in 15 mL of water and the suspension was heated at reflux. After 8 h, the reaction was cooled to 0 °C with ice and the precipitated catalyst was

filtered off. To the filtrate was added 30 mL of EtOAc and 30 mL of water. The aqueous layer was separated and concentrated to an orange solid/oil. This material was washed with 10 mL of MeOH and the insolubles filtered away. The product was precipitated from the MeOH with 20 mL of EtOAc to yield 650 mg (1.87 mmol) of an orange solid (50% yield, mp 208-212 °C, decomp). ^{1}H NMR (DMSO-d_6) δ 10.05 (H2, 1H, s), 9.71 (H4, 1H, s), 9.22 (H2′, 1H, d, J = 2 Hz), 8.76 (H6′, 1H, dd, J = 2 and 5 Hz), 8.53 (H5 or H8, 1H, d, J = 10 Hz), 8.47 (H5 or H8, 1H, d, J = 10 Hz), 8.42 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 8.29 (H6 or H7, 1H, dd, J = 8 and 10 Hz), 8.09 (H6 or H7, 1H, dd, J = 8 and 10 Hz), 7.68 (H5′, 1H, dd, J = 5 and 9 Hz), 4.71 (CH_3, 3H, s). Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.89; H, 3.75; N, 7.77.

2-Methyl-3-(3-pyridyl)isoquinolinium Iodide (2-8): A mixture of 4-bromo-2-methylisoquinolinium iodide[66] (379 mg, 1.08 mmol), 3-(tributylstannyl)pyridine (400 mg, 1.09 mmol), triphenylarsine (364 mg, 1.19 mmol) and trans-dibenzylideneacetone palladium(0) dimer (30 mg, 0.033 mmol) in 20 mL of degassed dry DMF stirred at 100 °C for 12 h under N_2. The reaction was cooled to room temperature and the insoluble catalyst was removed by filtration. The filtrate was concentrated to a brown solid/oil and washed with EtOAc (30 mL) to give an orange solid. The material was recrystallized with MeOH/EtOAc/Et_2O to give 190 mg of a slightly orange solid (51% yield, mp = 200-204 °C, decomp.). ^{1}H NMR (DMSO-d6): δ

10.07 (H1, 1H, s), 8.85 (H2′ and H3 and H6′, 3H, m), 8.58 (H4′, 1H, d, J = 9Hz), 8.26 (H5 or H8, 1H, t, J = 8 Hz), 8.10 (H6 and H7 and H5 or H8, 3H, m), 7.72 (H5′, 1H, dd, J = 6 and 9 Hz), 4.51 (CH_3, 3H, s). Anal. Calcd. for $C_{15}H_{13}N_2I$: Found C, 51.42; H, 3.71; N, 7.68: Calcd. C, 51.74; H, 3.76; N, 8.05.

1-Methyl-3′,4-bipyridinium Iodide (2-9): A solution of 4-chloro-1-methyl-pyridinium iodide (210 mg, 0.822 mmol), 3-(tributylstannyl)pyridine (400 mg, 1.09 mmol), and tris-dibenzylideneacetone palladium(0) dimer (40 mg, 0.041 mmol) in degassed DMF was heated at reflux for 24 h under N_2. The reaction was cooled to room temperature and the insolubles were filtered off. The product was precipitated from the filtrate by addition of EtOAc/Et_2O. The result was 50 mg of a red solid which was converted to the tetraphenylborate ion by dissolving the material in water and then precipitating with $NaBPh_4$. The result was a beige solid (20% yield, mp > 200 °C). See compound 3-20 for ^1H NMR.

Partially Deuteriated 5-Chloro-3,3′-bipyridine-1-oxide (2-10): The 3,5-dichloropyridine-1-oxide[55] contained 95% D at all positions.[55] The conditions were the same as those used for the preparation of 1. The reaction mixture stood for 20 h at room temperature and then was heated at reflux for 28 h. ^1H NMR (DMSO-d_6): 0% D at C-6, 95% D at C-4 and 65% D at C-2.

General Procedure for the N-Oxidation of Hetaryl Stannanes

3-(Tributylstannyl)pyridine N-Oxide (3-1): To $CHCl_3$ (20

mL) was added 3-(tributylstannyl)pyridine[79] (1.00 g, 2.72 mmol) and 57% 3-chloroperbenzoic acid (934 mg, 5.42 mmol). The solution was allowed to stir at 0 °C for 24 h. The $CHCl_3$ layer was washed twice with 20 mL of saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated to yield product. Purification by column chromatography with silica gel and elution with 90/10 EtOAc/MeOH gave 918 mg (2.38 mmol) of a slightly yellow oil (88% yield). ^1H NMR ($CDCl_3$): δ 8.20 (H2, 1H, s with Sn coupling side bands, J = 14 Hz), 8.15 (H6, 1H, d, J = 6 Hz), 7.20 (H4 and H5, 2H, m), 0.80-1.6 (27 H, m). Anal. Calcd for $C_{17}H_{31}NOSn$ .1/4 H_2O: C, 52.54; H, 8.17; N, 3.60. Found: C, 52.60; H, 8.18; N, 3.24.

3-(Tributylstannyl)quinoline-N-oxide(3-2): 3-(Tributylstannyl)quinoline[79] (580 mg, 1.39 mmol), 57-80% 3-chloroperbenzoic acid (660 mg, 3.83 mmol) and $CHCl_3$ yielded 530 mg (1.22 mmol) of a yellow oil (88% yield). ^1H NMR ($CDCl_3$): δ 8.72 (H2 or H4, 1H, s with Sn side bands, J = 8 Hz), 8.62 (H2 or H4, 1H, s with Sn coupling side bands, J = 7 Hz), 7.75 (H5 and H6 and H7 and H8, 4H, m), 0.80-1.6 (27 H, m). Anal. Calcd for $C_{21}H_{33}NOSn$: C, 58.09; H, 7.66; N, 3.23. Found: C, 58.17; H, 7.45; N, 2.84.

4-(Tributylstannyl)isoquinoline-N-oxide(3-3): 4-Tributyl stannylisoquinoline[79] (1.20 g, 2.76 mmol), 57-80% 3-chloroperbenzoic acid (1.14 g, 6.63 mmol), and $CHCl_3$ gave 960 mg (2.21 mmol) of a yellow oil (80% yield). ^1H NMR ($CDCl_3$): δ 8.74 (H1, 1H, s), 8.10 (H3, 1H, s with Sn coupling side

bands, J = 7 Hz), 7.62 (H5 and H6 and H7 and H8, 4H, m), 0.80-1.6 (27 H, m). Anal. Calcd for $C_{21}H_{33}NOSn$: C, 58.09; H, 7.66; N, 3.23. Found: C, 57.70; H, 7.39; N, 2.90.

1-Methyl-3-(tributylstannyl)pyridinium Iodide (3-4a) and Tetraphenylborate (3-4c): To diethyl ether (10 mL) was added 3-(tributystannyl)pyridine[79] (1.00 g, 2.71 mmol) and methyl iodide (5 mL, 16 mmol). The solution stood at room temperature for 4 h and then was concentrated to 1.38 g (2.70 mmol) of a yellow oil (100% yield). The oil solidified in a freezer at -8 ^{0}C. ^{1}H NMR ($CDCl_3$): δ 9.40 (H6, 1H, d, J = 6 Hz), 8.82 (H2, 1H, s with Sn coupling side bands, J = 7 Hz), 8.40 (H4, 1H, d with Sn coupling side bands J = 8 and 14 Hz), 8.05 (H5, 1H, dd, J = 6 and 8 Hz), 4.72 (CH_3, 3H, s), 0.8-1.6 (27 H, m). Anal. Calcd for $C_{18}H_{34}NSnI$: C, 42.38; H, 6.72; N, 2.75. Found: C, 42.06; H, 6.82; N, 2.61.

To 1-methyl-3-(tributylstannyl)pyridinium iodide (3-4a) (1.20 g, 2.35 mmol) in 20 mL of diethyl ether was added a saturated solution of sodium tetraphenylborate in 9 to 1 diethyl ether-acetone until the yellow color disappeared (approx. 25 mL). The white solid was collected and washed with 50 mL of water to give after drying 1.60 g (2.27 mmol) of white product (97% yield, mp 146-152 °C). ^{1}H NMR (DMSO-d_6): δ 8.81 (H2 and H6, 2H, m), 8.55 (H4, 1H, d, J = 8 Hz), 7.98 (H5, 1H, t, J = 8 Hz), 7.16-6.74 (Ph, 20H, m), 4.28 (CH_3, 3H, s), 0.8-1.6 (27 H, m).

1-Methyl-3-(tributylstannyl)pyridinium Tosylate (3-4b): To EtOAc (20 mL) was added 3-(tributylstannyl)pyridine[79] (1.00 g, 2.71 mmol) and methyl tosylate (606 mg, 3.25 mmol). The solution was stirred at reflux and monitored by TLC until starting material was consumed. After 8 h the reaction was complete and 1 gram of poly-4-vinylpyridine resin was added to remove excess methyl tosylate. The suspension was stirred at reflux for 4 h, then filtered and concentrated to 1.35 grams (2.43 mmol) of a slightly brown oil (90% yield). ^{1}H NMR ($CDCl_3$): δ 9.20 (H6, 1H, d, J = 6 Hz), 8.68 (H2, 1H, s with Sn coupling side bands, J = 7 Hz), 8.28 (H4, 1H, d with Sn coupling side bands, J = 8 and 14 Hz), 7.92 (H5, 1H, dd, J = 6 and 8 Hz), 7.70 (Ph, 2H, d, J = 9 Hz), 7.11 (Ph, 2H, d, J = 9 Hz), 4.53 (CH_3, 3H, s), 2.33 (CH_3, 3H, s), 0.80-1.6 (27 H, m). Anal. Calcd for $C_{25}H_{41}NO_3SSn$: C, 54.16; H, 7.46; N; 2.53. Found: C, 53.99; H, 7.70; N, 2.43.

1-Methyl-3-(tributylstannyl)quinolinium Iodide (3-5): To Et_2O (10 mL) was added 3-(tributylstannyl)quinoline[79] (810 mg, 1.94 mmol) and methyl iodide (5 mL, 16 mmol). The solution was allowed to remain at room temperature for 4 h to deposit the product and then was cooled in a refrigerator overnight. The solid was collected and dried to give 1.0 g (1.79 mmol) of yellow crystals (92% yield). ^{1}H NMR ($CDCl_3$): δ 10.04 (H2, 1H, s with Sn coupling side bands, J = 7 Hz), 8.87 (H4, 1H, s with Sn coupling side bands, J = 14 Hz), 8.45 (H5 or H8, 1H, d, J = 9 Hz), 8.20 (H5 or H6 and H6 or H7, 2H, m), 7.98 (H6 or H7,

1H, t, J = 9 Hz) 4.97 (CH_3, 3H, s), 0.8-1.6 (27 H, m). Anal. Calcd for $C_{22}H_{36}NSnI$: C, 47.17; H, 6.48; N, 2.50. Found: C, 47.56; H, 6.51; N, 2.52.

1-Methyl-4-(tributylstannyl)pyridinium Iodide (3-6a): To Et_2O (10 mL) was added 4-(tributystannyl)pyridine[79] (300 mg, 0.813 mmol) and methyl iodide (5 mL, 16 mmol). The solution stood at room temperature for 6 h and then was concentrated to 400 mg (0.783 mmol) of a slightly yellow oil (96% yield). The oil solidified in a freezer at -8 °C. ^1H NMR ($CDCl_3$): δ 9.18 (H2, 2H, d, J = 7 Hz), 8.10 (H3, 2H, d with Sn coupling side bands, J = 7 Hz), 4.72 (CH_3, 3H, s), 0.8-1.6 (27 H, m). Anal. Calcd for $C_{18}H_{34}NSnI$: C, 42.38; H, 6.72; N, 2.75. Found: C, 42.07; H, 6.85; N, 2.65.

1-Methyl-4-(tributylstannyl)pyridinium Tosylate (3-6b): To ethyl acetate (20 mL) was added 4-(tributylstannyl)pyridine[79] (565 mg, 1.53 mmol) and methyl tosylate (400 mg, 2.15 mmol). The solution was stirred at reflux and monitored by TLC until starting material was consumed. After 18 h the reaction was complete and 1 gram of poly-4-vinylpyridine was added to remove excess methyl tosylate. The suspension was stirred at reflux for 2 h, then filtered and concentrated to 800 mg (1.44 mmol) of a clear oil (93% yield). ^1H NMR ($CDCl_3$): δ 9.18 (H2, 2H, d, J = 7 Hz), 8.10 (H3, 2H, d with Sn coupling side bands, J = 7Hz), 7.77 (Ph, 2H, d, J = 9 Hz), 7.34 (Ph, 2H, d, J = 9 Hz), 4.49 (CH_3, 3H, s), 2.31 (CH_3, 3H, s), 0.80-1.6 (27 H, m). Anal. Calcd for

$C_{25}H_{41}NO_3SSn$: C, 54.16; H, 7.46; N; 2.53. Found: C, 54.37; H, 7.80; N, 2.44.

General Procedure for the Cross-Coupling of Hetaryl Stannyl N-Oxides with Stannane as the Limiting Reagent

A mixture of a stannyl-N-oxide (2.5 mmol), hetaryl halide (3.0 mmol), and Pd-catalyst (0.25 mmol) in solvent degassed by N_2 bubbling was allowed to stir at reflux until the starting material was consumed (TLC analysis) (12-24 h). The reaction was cooled to 0 °C and the insoluble material was removed. (Work up A) The filtrate was concentrated and then dissolved in 50 ml of MeOH. The insoluble materials were filtered off and the filtrate was concentrated onto approx. 25 g of silica gel. The resultant solid was added to the top of a silica gel column and eluted with the appropriate solvent system. The product was washed with 50 mL of EtOAc and dried under vacuum. (Work up B) To the filtrate was added 25 mL of EtOAc. The filtrate was washed with two 25 mL portions of water. The aqueous extracts were combined and concentrated to yield product. The product was washed with 50 mL of EtOAc and dried under vacuum.

3-(3-Quinolyl)pyridine N-Oxide (3-7): 3-Bromoquinoline (0.250 mL, 1.81 mmol), 3-(tributylstannyl)pyridine-N-oxide (3-1) (580 mg, 1.51 mmol), and tetrakistriphenylphosphine palladium(0) (200 mg, 0.173 mmol) were heated in DMF (30 mL). Work up A (pg 102) was used with an eluant of 90/10 EtOAc/MeOH

to give 220 mg (0.990 mmol) of an orange solid (66% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6: δ 9.26 (H2′, 1H, s), 8.81 (H2 and H4′, 2H, m,), 8.28 (H6, 1H, d, J = 6 Hz), 8.05 (H4 and H5′ or H8′, 2H, m,), 7.84 (H5′ or H8′ and H6′ or H7′, 2H, m,), 7.67 (H6′ or H7′, 1H, t, J = 9 Hz), 7.56 (H5, 1H, dd, J = 6 and 9 Hz). Anal. Calcd for $C_{14}H_{10}N_2O \cdot 1.25\ H_2O$: C, 68.14; H, 5.11; N, 11.35. Found: C, 68.62; H, 4.77; N, 11.30.

3-(4-Isoquinolyl)pyridine N-Oxide (3-8): 4-Bromoisoquinoline (500 mg, 2.40 mmol), 3-(tributylstannyl)pyridine-N-oxide (3-1) (920 mg, 2.40 mmol), and tetrakis(triphenyl phosphine)palladium(0) (300 mg, 0.260 mmol) were heated in dry, degassed DMF (30 mL). Work up A (pg 102) was used with a eluant of 90/10 EtOAc/MeOH to give 228 mg (1.03 mmol) of a yellow solid(43% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6): δ 9.72 (H1′, 1H, s), 8.68 (H3′, 1H, s), 8.51 (H2, 1H, d, J = 2 Hz), 8.45 (H6 and H5′ or H8′, 2H, m), 7.9-8.1 (H6′ and H7′ and H5′ or H8′, 3H, m), 7.65 (H4 and H5, 2H, m). Anal. Calcd for $C_{14}H_{10}N_2O\ .H_2O$: C, 69.40; H, 4.99; N,11.57. Found:: C, 69.11; H, 4.76; N, 11.48.

3-(5-Pyrimidyl)pyridine N-Oxide (3-9): 5-Bromopyrimidine (155 mg, 0.976 mmol), 3-(tributylstannyl)pyridine-N-oxide (3-1) (375 mg, 0.976 mmol), and tetrakis(triphenylphosphine) palladium(0) (200 mg, 0.173 mmol) were heated in THF (30 mL). Work up B (pg 102) gave 108 mg (0.624 mmol) of a white solid (64% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6): δ 9.24 (H2′, 1H, s), 9.19 (H4′ and H6′, 2H, s), 8.78 (H2, 1H, s), 8.29 (H6, 1H,

d, J = 5 Hz), 7.77 (H4, 1H, d, J = 9 Hz), 7.55 (H5, 1H, dd, J = 5 and 9 Hz). Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H,4.07; N, 24.27. Found: C, 61.97; H, 4.03; N, 23.87.

3-(5-Pyrimidyl)quinoline N-Oxide (3-10): 5-Bromopyrimidine (250 mg, 1.57 mmol), 3-(tributylstannyl)quinoline-N-oxide (3-2) (530 mg, 1.22 mmol), tetrakis(triphenyl phosphine) palladium(0) (250 mg, 0.216 mmol) and toluene (30 mL) were heated. Work up B (pg 102) gave 140 mg (0.627 mmol) of a white solid (51% yield, mp > 200 °C). ^{1}H NMR in DMSO-d_6: δ 9.31 (H4′ and H6′, 2H, s), 9.25 (H2′ or H2, 1H, s), 9.16 (H2′ or H2, 1H, s), 8.53 (H5 or H8, 1H, d, J = 9 Hz), 8.43 (H4, 1H, s), 8.12 (H5 or H8, 1H, d, J = 9 Hz), 7.85 (H6 and H7, 2H, m,). Anal. Calcd for $C_{14}H_{10}N_3O$ .3/4 H_2O: C, 65.95; H, 4.47; N, 17.75. Found: C,66.09; H, 3.99; N, 17.32.

4-(5-Pyrimidyl)isoquinoline N-Oxide (3-11): 5-Bromopyrimidine (250 mg, 1.57 mmol), 4-(tributylstannyl) isoquinoline-N-oxide (3-3) (350 mg, 0.772 mmol), tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.087 mmol) and dry, degassed toluene were heated (30 mL). Work up A (pg 102) yielded 100 mg (0.450 mmol) of a white solid (58% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6): δ 9.42 (H1, 1H, s), 8.95 (H4′ and H6′, 2H, s,), 8.88 (H2′, 1H, s), 8.19 (H3, 1H, s), 7.88 (H5 or H8, 1H, d, J = 8 Hz), 7.79 (H6 and H7 and H5 or H8, 3H, m). Anal. Calc'd for $C_{14}H_{10}N_3O$ .3/4 H_2O: C,65.95; H, 4.47; N, 17.75. Found: C,65.85; H, 3.99; N, 17.30.

Cross-coupling of an N-Oxide with Excess Stannane

3-(2-Pyrazinyl)pyridine N-oxide (3-12): To 10 mL of THF was added 2-chloropyrazine (0.078 mL, 0.87 mmol) and tetrakis(triphenylphosphine) palladium(0) (100 mg, 0.087 mmol); the solution was heated at reflux for 1 h while stirring. To this 3-(tributylstannyl)pyridine-N-oxide (3-1) (403 mg, 1.05 mmol) in dry THF (10 mL) was slowly added over 2 h. The solution was stirred at reflux with 4 subsequent additions of the stannane (84 mg, 0.22 mmol) in 1 mL of THF every 2 h. The reaction was cooled to room temperature when the chloropyrazine was consumed (TLC, 36 h). The mixture was concentrated to a brown oil which was chromatographed with 90% EtOAc and 10% MeOH to give 148 mg (0.855 mmol) of a white solid (98% yield, mp 166-168 °C). ^{1}H NMR (DMSO-d_6): δ 8.35 (H3′, 1H, s), 8.93 (H2, 1H, d, J = 1 Hz), 8.75 (H5′ and H6′, 2H, m), 8.34 (H6, 1H, dd, J = 1 and 6 Hz), 8.07 (H4, 1H, dt, J = 1, 1 and 9 Hz), 5.60 (H5, 1H, dd, J = 6 and 9 Hz). Anal. Calcd for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.78; H, 4.07; N, 24.09.

General Procedure for the Cross-Coupling of Quaternized Hetaryl Stannanes with Stannane as the Limiting Reagent

A mixture of haloheteroarene (2.0 mmol), solvent (20 mL) and Pd catalyst (0.15 mmol) was stirred at reflux for 1 h. The quaternized stannane (1.5 mmol) dissolved in 10 mL of solvent was added slowly over a 2-4 h period. The reaction was allowed to stir at reflux until starting material was consumed (TLC).

(Work up A) The insoluble materials were filtered off and washed with 30 mL of MeOH. The solid was dissolved in 50 mL of acetone, the residual material was removed and the filtrate was concentrated to a solid and washed with EtOAc. (Work up B) The reaction was cooled and to it was added 50 mL of water and 50 mL of EtOAc. The layers were separated and the aqueous layer was concentrated. The material was taken up in a minimum amount of EtOH and then made cloudy with EtOAc. The cloudy solution was cooled to 0 °C and the product was collected and dried under vacuum. (Work up C) The mixture of insoluble materials from the reaction mixture was filtered and then washed with 20 mL of cold acetonitrile to recover soluble monoquaternized product. Following filtration and concentration of the wash, the resultant solid was recrystallized from EtOH/$CHCl_3$/EtOAc to yield product.

1-Methyl-3-(3-pyridyl)quinolinium Iodide (3-13): 3-Iodo pyridine (130 mg, 0.626 mmol), tetrakis(triphenylphosphine) palladium(0) (100 mg. 0.086 mmol), 1-methyl-3-(tributyl-stannyl)quinolinium iodide (3-5) (350 mg, 0.625 mmol) were heated in 30 mL of THF. Work up B (pg 106) gave 33 mg (0.095 mmol) of a red solid (15% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6): δ 10.05 (H2, 1H, s), 9.71 (H4, 1H, s), 9.22 (H2′, 1H, d, J = 2 Hz), 8.76 (H6′, 1H, dd, J = 2 and 5 Hz), 8.53 (H5 or H8, 1H, d, J = 10 Hz), 8.47 (H5 or H8, 1H, d, J = 10 Hz), 8.42 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 8.29 (H6 or H7, 1H, dd, J = 8 and 10 Hz), 8.09 (H6 or H7, 1H, dd, J = 8 and 10 Hz), 7.68

(H5′, 1H, dd, J = 5 and 9 Hz), 4.71 (s, 3H). Anal. Calcd. for $C_{15}H_{13}N_2I$: C, 51.74; H, 3.76; N, 8.05. Found: C, 51.89; H, 3.75; N, 7.77.

1-Methyl-3-(5-pyrimidyl)pyridinium Tetraphenylborate (3-14): 5-Bromopyrimidine (200 mg, 1.14 mmol), 1-methyl-3-(tributylstannyl)pyridinium tetraphenylborate (400 mg, 0.570 mmol), and tetrakis(triphenylphosphine) palladium(0) (100 mg, 0.087 mmol) were heated in toluene (30 mL). Work up A (pg 106) gave 154 mg (0.313 mmol) of an orange solid (55% yield, mp >200 ^{0}C). ^{1}H NMR (DMSO-d_6): δ 9.58 (H2, 1H, s), 9.38 (H2′, 1H, s), 9.35 (H4′ and H6′, 2H, s), 9.00 (H4 and H6, 2H, m), 8.25 (H5, 1H, dd, J = 6 and 9 Hz), 7.20-6.78 (Ph, 20 H, m) 4.40 (CH_3, 3H, s). Anal. Calcd for $C_{34}H_{30}N_3B$: C, 83.10; H, 6.15; N, 8.10. Found: C, 83.52; H, 6.25; N, 8.55.

1-Methyl-3-(2-pyrazinyl)pyridinium Tetraphenylborate (3-15a): 2-Chloropyrazine (0.200 mL, 2.24 mmol), 1-methyl-3-(tributylstannyl)pyridinium tetraphenylborate (500 mg, 0.570 mmol), and tetrakis(triphenylphosphine) palladium(0) (100 mg, 0.087 mmol) were heated in toluene (30 mL). Work up A (pg 106) gave 81 mg (0.165 mmol) of an orange solid (29% yield, mp >200 ^{0}C). ^{1}H NMR (DMSO-d_6): δ 9.71 (H2, 1H, s), 9.46 (H3′, 1H, s), 9.20 (H4, 1H, d, J = 9 Hz), 9.03 (H6, 1H, d, J = 6 Hz), 8.85 (H4′ and H6′, 2H, m), 8.20 (H5, 1H, dd, J = 6 and 9 Hz), 7.20-6.78 (Ph, 20H, m) 4.40 (CH_3, 3H, s). Anal. Calcd for $C_{34}H_{30}N_3B$ 1/4 H_2O: C, 82.34; H, 6.20; N, 8.47. Found: C, 82.54; H, 6.22; N, 7.99.

1-Methyl-3-phenylpyridinium Tetraphenylborate (3-16): 1-Methyl-3-(tributylstannyl)pyridinium tetraphenylborate (300 mg, 0.427 mmol), 1,2-bis(diphenylphosphino)ethane palladium(II) dichloride (30 mg, 0.052 mmol), sodium tetraphenylborate (146 mg, 0.427 mmol), were heated to reflux in THF (20 mL). Work up: The insolubles were filtered off and the filtrate was concentrated to an oil/solid which was washed with 10 mL of 5:1 EtOAc:Et_2O. The insolubles were filtered off to give 128 mg (0.275 mmol) of a orange solid (64% yield, mp > 200 °C). Product was verified by comparison of its proton NMR spectrum with that of an authentic sample.[69] ^{1}H NMR (DMSO-d_6): δ 9.58 (H2, 1H, s), 9.20 (H6, 1H, d, J = 6 Hz), 8.95 (H4, 1H, d, J = 9 Hz), 8.35 (H5, 1H, dd, J = 6 and 9 Hz), 7.80-7.60 (Ph, 5H, m), 7.20-6.78 (Ph, 20 H, m), 4.40 (CH_3, 3H, s). Carlton D. Dill synthesized the hexafluorophosphate by another route.[69]

1-Methyl-3-(3-quinolinyl)pyridinium Perchlorate (3-17a): 3-Bromoquinoline (0.270 mL, 1.99 mmol), 1-methyl-3-(tributylstannyl)pyridinium tosylate (770 mg, 1.43 mmol), and tetrakis(triphenylphosphine)palladium(0) were heated in toluene (30 mL). Work up B (pg 106) gave 300 mg (0.764 mmol) of an orange solid (mp 178-182 °C, 54% yield). ^{1}H NMR (DMSO-d_6): δ 9.63 (H2 or H2′, 1H, s), 9.38 (H2 or H2′, 1H, s), 9.08 (H4, 1H, d, J = 9 Hz), 9.02 (H6, 1H, d, J = 6 Hz), 8.93 (H4′, 1H, s), 8.27 (H5, 1H, dd, J = 6 and 9 Hz), 8.10 (H5′ and H8′, 2H, t, J = 10 Hz), 7.90 (H6′ or H8′, 1H, dd, J = 8 and 10

Hz), 7.73 (H6′ or H8′, 1H, dd, J = 8 and 10 Hz), 7.45 (Ph, 2H, d, J = 9 Hz), 7.06 (Ph, 2H, d, J = 9 Hz), 4.44 (CH_3, 3H, s), 2.25 (CH_3, 3H, s). A small portion of the material was converted to the perchlorate salt by dissolving it in hot aqueous sodium perchlorate. The solution was cooled to 0 °C and the precipitate was collected and dried under a vacuum (mp > 200 °C). Anal. Calcd for $C_{15}H_{13}N_2O_4Cl$: C, 56.17; H, 4.08; N, 8.74. Found: C, 56.06; H, 4.09; N, 8.69. We made the iodide by another route.[69]

1-Methyl-4-(3-quinolinyl)pyridinium Tosylate and Perchlorate (3-18): 3-Bromoquinoline (300 mg, 1.46 mmol), 1-methyl-4-(tributylstannyl)pyridinium tosylate (400 mg, 0.720 mmol), and tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.087 mmol) were heated in THF (30 mL). Work up C (page 106) gave 153 mg (0.389 mmol) of green crystals (mp 189-191 °C, 54% yield). ^{1}H NMR (DMSO-d_6): δ 9.53 (H2′, 1H, s), 9.19 (H4′, 1H, s), 9.11 (H2, 2H, d, J = 7 Hz), 8.72 (H3, 2H, d, J = 7 Hz), 8.15 (H5′ and H8′, 2H, m), 7.95 (H6′ or H7′, 1H, dd, J = 8 and 10 Hz), 7.75 (H6′ or H7′, 1H, dd, J = 8 and 10 Hz), 7.48 (Ph, 2H, d, J = 9 Hz), 7.09 (Ph, 2H, d, J = 9 Hz), 4.37 (CH_3, 3H, s), 2.25 (CH_3, 3H, s). A small portion of the material was converted to the perchlorate salt by dissolving it in hot aqueous sodium perchlorate. The solution was cooled to 0 °C and the precipitate was collected and dried under a vacuum (mp > 200 °C). Anal. Calcd for $C_{15}H_{13}N_2O_4Cl$: C, 56.17; H, 4.08; N, 8.74. Found: C, 56.23; H, 4.09; N, 8.65.

1-Methyl-4-(5-pyrimidyl)pyridinium Tosylate (3-19): 5-Bromopyrimidine (300 mg, 1.89 mmol), 1-methyl-4-(tributylstannyl)pyridinium tosylate (520 mg, 0.936 mmol), and tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.173 mmol) were heated in toluene (30 mL). Work up C (pg 106) gave 238 mg (0.693 mmol) of a red crystals (74% yield, mp 179-181 ^{0}C). ^{1}H NMR (DMSO-d_6): δ 9.49 (H4′ and H6′, 2H, s), 9.42 (H2′, 1H, s), 9.15 (H2, 2H, d, J = 7 Hz), 8.65 (H3, 2H, d, J = 7 Hz), 7.46 (Ph, 2H, d, J = 9 Hz), 7.10 (Ph, 2H, d, J = 9 Hz), 4.37 (CH_3, 3H, s), 2.28 (CH_3, 3H, s). Anal. Calcd for $C_{17}H_{17}N_3O_3S$ .1/2 H_2O: C, 57.94; H, 5.15; N, 11.92. Found: C, 57.90; H, 5.13; N, 11.69.

1-Methyl-4-(3-pyridyl)pyridinium Tetraphenylborate (3-20): 3-Iodopyridine (518 mg, 2.53 mmol), 1-methyl-4-(tributylstannyl)pyridinium tosylate (700 mg, 1.26 mmol), copper(I) iodide (66 mg, 0.35 mmol) and tetrakis(triphenylphosphine) palladium(0) (200 mg, 0.173 mmol) were placed in 20 mL of DMF. The suspension was heated to 80 °C for 1 h to give a solution which was allowed to stir at room temperature overnight. Following filtration, the filtrate was concentrated under reduced pressure to a brown oil which was dissolved in 10 mL of MeOH; the insolubles were filtered off. The MeOH phase was concentrated and the product was converted to the tetraphenylborate salt by dissolving it in 10 mL of water and then adding sodium tetraphenylborate (430 mg, 1.26 mmol). The product was filtered off and dried in vacuo to give 390 mg of

a slightly orange solid (64% yield, mp > 200 °C). ^{1}H NMR (DMSO-d_6): δ 9.26 (H2′, 1H, d, J = 2 Hz), 9.07 (H2, 2H, d, J = 7 Hz), 8.82 (H6′, 1H, dd, J = 2 and 6 Hz), 8.58 (H3, 2H, d, J = 7 Hz), 8.47 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 7.68 (H5′, 1H, dd, J = 6 and 9 Hz), 7.17-6.76 (20 H, m), 4.34 (CH_3, 3H, m). Anal. Calcd for $C_{34}H_{31}N_2B$: C, 85.71; H, 6.37; N, 5.71. Found: C, 85.53; H, 6.37; N, 5.63.

General Procedure for the Cross-Coupling of N-Quaternized Stannanes with the Hetaryl Halide as the Limiting Reagent

A mixture of haloheteroarene (1.0 mmol), toluene (20 mL) and Pd catalyst (0.15 mmol) are stirred at reflux for 1 h. The quaternized stannane (1.5 mmol) dissolved in 10 mL of toluene was added slowly over a 2 h period. The reaction was allowed to stir at reflux with periodic additions of stannane (0.25 mmol, usually 3-4 additions) until starting material was consumed (TLC). (Work up A) The insoluble materials were filtered off and washed with 30 mL of EtOH. The EtOH soluble was separated from the insolubles (black Pd) and concentrated down. The resultant material is then washed with 20 mL of acetonitrile and the insolubles are filtered off. The filtrate was concentrated down to yield product. If necessary the product was recrystallized with EtOH/$CHCl_3$/Et_2O. (Work up B) Same as the above but if resultant product was an oil, then it was converted to the perchlorate salt by dissolving the oil in

hot, saturated, aqueous sodium perchlorate. Upon cooling the product precipitated and was recovered by filtration.

1-Methyl-3-(2-pyrazinyl)pyridinium Tosylate (3-15b): 2-Chloropyrazine (0.040 mL, 0.44 mmol), 1-methyl-3-(tributylstannyl)pyridinium tosylate (291 mg, 0.524 mmol), and $Pd(dppe)Cl_2$ (40 mg, 0.069 mmol) were heated in dry, degassed toluene (15 mL). Work up A (pg 112) gave 130 mg (0.379 mmol) of slightly brown crystals (87% yield, mp 164-167 ^{0}C). ^{1}H NMR (CD_3OD): δ 9.69 (H2, 1H, s), 9.36 (H3′, 1H, d, J = 1 Hz), 9.24 (H4, 1H, d, J = 9 Hz), 8.97 (H6, 1H, d, J = 6 Hz), 8.83 (H5′, 1H, dd, J = 1 and 3 Hz), 8.76 (H6′, 1H, d, J = 3 Hz), 8.20 (H5, 1H, dd, J = 6 and 9 Hz), 7.65 (Ph, 2H, d, J = 9 Hz), 7.20 (Ph, 2H, d, J = 9 Hz), 4.40 (CH_3, 3H, s), 2.34 (CH_3, 3H, s). Anal. Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.22; H, 5.02; N, 11.82.

1-Methyl-3-(3-quinolinyl)pyridinium Tosylate (3-17b): 3-Bromoquinoline (0.090 mL, 0.673 mmol), 1-methyl-3-(tributylstannyl)pyridinium tosylate (465 mg, 0.837 mmol), and $Pd(dppe)Cl_2$ (40 mg, 0.069 mmol) were heated in toluene (15 mL). Work up A (pg 112) gave 230 mg (0.586 mmol) of an slightly brown solid (mp 184-186 °C, 87% yield). ^{1}H NMR (DMSO-d_6): δ 9.63 (H2 or H2′, 1H, s), 9.38 (H2 or H2′, 1H, s), 9.08 (H4, 1H, d, J = 9 Hz), 9.02 (H6, 1H, d, J = 6 Hz), 8.93 (H4′ 1H, s), 8.27 (H5, 1H, dd, J = 6 and 9 Hz), 8.10 (H5′ and H8′, 2H, t, J = 10 Hz), 7.90 (H6′ or H7′, 1H, dd, J = 8 and 10 Hz), 7.73 (H6′ or H7′, 1H, dd, J = 8 and 10 Hz), 7.45 (Ph, 2H,

d, J = 9 Hz), 7.06 (Ph, 2H, d, J = 9 Hz), 4.44 (CH_3, 3H, m), 2.25 (CH_3, 3H, m). Anal. Calcd for $C_{22}H_{20}N_2O_3S$ .1\2 H_2O: C, 65.81; H, 5.27; N, 6.98. Found: C, 66.08; H, 5.16; N, 6.87.

1-Methyl-3-(4-isoquinolinyl)pyridinium Perchlorate (3-21): 4-Bromoisoquinoline (100 mg, 0.488 mmol), 1-methyl-3-(tributylstannyl)pyridinium tosylate (677 mg, 1.22 mmol), and Pd(dppe)Cl_2 (30 mg, 0.049 mmol) were heated in toluene (20 mL). Work up B (page 112) gave 110 mg (0.343 mmol) of a slightly yellow solid (mp > 200 °C, 70% yield). ^{1}H NMR (DMSO-d_6): δ 9.52 (H1′ or H2, 1H, s), 9.36 (H1′ or H2, 1H, s), 9.12 (H6, 1H, d, J = 6 Hz), 8.84 (H4, 1H, d, J = 8 Hz), 8.61 (H3′, 1H, s), 8.33 (H5 and H5′ or H8′, 2H, m), 7.86 (H6′ and H7′ and H5′ or H8′, 3H, m), 4.44 (CH_3, 3H, m). Anal. Calcd for $C_{15}H_{13}N_2O_4Cl$ .1\4 H_2O: C, 55.39; H, 4.18; N, 8.61. Found: C, 55.03; H, 3.98; N, 8.49. We prepared the iodide by another route.[69]

1-Methyl-4-(4-isoquinolinyl)pyridinium Perchlorate (3-22): 4-Bromoisoquinoline (100 mg, 0.488 mmol), 1-methyl-4-(tributylstannyl)pyridinium tosylate (677 mg, 1.22 mmol), and 1,2-(diphenylphosphinoethane)Palladium(II) dichloride (30 mg, 0.049 mmol) were heated in toluene (20 mL). Work up B (page 112) gave 125 mg (0.390 mmol) of a slighty brown solid (mp > 200 °C, 80% yield). ^{1}H NMR (DMSO-d_6): δ 9.55 (H1′ or H3′, 1H, s), 9.15 (H2, 2H, d, J = 7 Hz), 8.65 (H1′ or H3′, 1H, s), 8.42 (H3, 2H, d, J = 7 Hz), 8.34 (H5′ or H8′, 1H, d, J = 8 Hz), 7.90 (H6′ and H7′ and H5′ or H8′, 3H, m), 4.35 (CH_3, 3H, m).

Anal. Calcd for $C_{15}H_{13}N_2O_4Cl$: C, 56.17; H, 4.08; N, 8.74. Found: C, 56.47; H, 4.10; N, 8.71.

5-Carbamoyl-2,3'-bipyridine (4-1): Diethyl(3-pyridyl) borane (0.809 g, 5.50 mmol), 6-chloronicotinamide (1.04 g, 6.64 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.683 g, 0.591 mmol) were added to 25 mL of degassed THF. After stirring for 5 min, potassium carbonate (1.61 g, 11.6 mmol) dissolved in 13 mL of degassed water was added and the solution was stirred at reflux for 6 h. The reaction mixture was cooled to 0 °C and the catalyst was removed under nitrogen. To the filtrate, 50 mL of EtOAc was added and the aqueous layer was removed. The organic layer was extracted twice with 10 mL portions of 2M HCl. The acid washes were combined and made basic with sodium carbonate to give a precipitate which was collected and recrystallized from water to afford 1.01 g (5.07 mmol, 92% yield) of a white solid (mp 227-229 °C decomp.). ^{1}H NMR (DMSO-d_6) δ 9.25 (H2', 1H, s), 9.15 (H6, 1H, d, J = 2 Hz), 8.63 (H6', 1H, dd, J = 2 and 6 Hz), 8.50 (H4', 1H, dd, J = 2 and 8 Hz), 8.36 (H4, 1H, dd, J = 2 and 8 Hz), 8.07 (H3, 1H, d, J = 8 Hz), 7.60 (H5', 1H, dd, J = 6 and 8 Hz). Anal Calcd. for $C_{11}H_9ON_3$ .1/4H_2O: C, 64.86: H, 4.70; N, 20.63. Found: C, 65.24; H, 4.50; N, 20.93.

5-Carbamoyl-1'-methyl-2,3'-bipyridinium Iodide (4-2a): Compound 4-1 and excess MeI in EtOAc gave crystals of 4-2 after stirring at room temperature overnight. Trituration with hot methanol yielded pale yellow crystals (80% yield, mp >250

°C). ^{1}H NMR (CD_3OD) δ 9.47 (H2′, 1H, s), 9.13 (H6, 1H, d, J = 2 Hz), 9.07 (H4′, 1H, d, J = 8 Hz), 8.92 (H6′, 1H, d, J = 6 Hz), 8.42 (H5′, 1H, dd, J = 6 and 8 Hz), 8.22 (H4, 1H, dd, J = 2 and 8 Hz), 8.15 (H3, 1H, d, J = 8 Hz), 4.52 (CH_3, 3H, s). Anal. Calcd. for $C_{12}H_{12}ON_3I$: C, 42.25; H, 3.55; N, 12.32. Found: C, 42.01; H, 3.54; N, 12.61.

5-Carbamoyl-1′-methyl-2,3′-bipyridinium Tosylate (4-2b): Compound 4-1 and excess MeOTs in CH_3CN gave crystals of 4-2 after stirring at reflux overnight. Filtration of the hot solution and then two washes with hot CH_3CN gave beige crystals (99% yield, mp 185-192 °C, decomp.). ^{1}H NMR (DMSO-d_6) δ 9.71 (H2′, 1H, s), 9.20 (H6 and H6′, 2H, m), 9.03 (H4 or H4′, 1H, d, J = 6 Hz), 8.46 (H4 or H4′, 1H, dd, J = 2 and 9 Hz), 8.33 (NH and H3, 2H, bd, J = 9 Hz), 8.23 (H5′, 1H, dd, J= 6 and 9 Hz), 7.75 (NH, 1H, bs), 7.45 (Ph, 2H, d, J = 9 Hz), 7.08 (Ph, 2H, d, J = 9 Hz) 4.44 (CH_3, 3H, s), 2.26 (CH_3, 3H, s). Anal. Calcd. for $C_{19}H_{19}O_4N_3S$: C, 59.20; H, 4.97; N, 10.90. Found: C, 58.85; H, 4.90; N, 10.80.

5-Carbamoyl-1,1′-dimethyl-2,3′-bipyridinium Diiodide (4-3a): Salt 4-2 was dissolved in dry DMF with excess MeI and heated to 95 °C in a sealed tube overnight. The tube was cooled and the solids were collected. The solids were triturated with hot methanol to give orange needle-like crystals which were recrystallized from water and isopropyl alcohol to yield (25%) of orange needle-like crystals (mp >250 °C). ^{1}H NMR (D_2O) δ 9.60 (H2′ or H6, 1H, s), 9.35 (H2′ or H6,

1H, s), 9.20 (H4 or H4′, 1H, d, J = 8 Hz), 9.13 (H6′, 1H, d, J = 6 Hz), 8.94 (H4 or H4′, 1H, d, J = 8 Hz), 8.43 (H5′, 1H, dd, J = 6 and 8 Hz), 8.36 (H3, 1H, d, J = 8 Hz), 4.6 (CH_3, 3H, s), 4.38 (CH_3, 3H, s). Anal. Calcd. for $C_{13}H_{16}ON_3I_2$ .1/2H_2O: C, 31.73; H, 3.28; N, 8.54. Found: C, 31.59; H, 3.18; N, 8.48.

5-Carbamoyl-1,1′-dimethyl-2,3′-bipyridinium Ditosylate (4-3b): Salt 4-2 (0.519 mmol) was added to distilled sulfolane (10 mL) with MeOTs (0.887 mmol) and stirred overnight at 110 °C. The solution was cooled and the product precipitated with 1:1 EtOAc/Et_2O. The product was collected and recrystallized with MeOH and EtOAc to give 249 mg (0.436 mmol) of an off-white solid (84% yield, mp >200 °C). H^1 NMR (DMSO-d_6), δ 9.65 (H2′ or H6, 1H, s), 9.36 (H4′ or H6, 1H, s), 9.21 (H6′, 1H, d, J = 5 Hz), 9.05 (H4 or H4′, 1H, d, J = 8 Hz), 8.85 (H4 or H4′, 1H, d, J = 8 Hz), 8.65 (NH, 1H, s), 8.37-8.27 (NH and H5′ and H3, 3H, m), 7.42 (Ph, 4H, d, J = 8 Hz), 7.08 (Ph, 4H, d, J = 8 Hz), 4.42 (CH_3, 3H, s), 4.24 (CH_3, 3H, s), 2.26 (CH_3, 6H, s). Anal. Calcd. for $C_{27}H_{29}O_7N_3S_2$ .H_2O: C, 54.99; H, 5.29; N, 7.13. Found: C, 55.24; H, 4.98; N, 6.99.

5-Carbamoyl-1′-(2-(4-nitrophenyl)ethyl)-2,3′-bipyridinium Iodide (4-4): A mixture of 1.52 g (6.61 mmol) of 2-(4-nitrophenyl)ethyl bromide and 3 g (20 mmol) of NaI in 20 mL of acetone was stirred at reflux. The suspension was allowed to cool and the insoluble materials were removed. The filtrate was concentrated and 20 mL of EtOAc was added. The insoluble solids were removed and the filtrate was

concentrated to yield p-nitrophenethyl iodide. This was dissolved in 25 mL of 1,4-dioxane and to this 1.3 g of 4-1 (6.5 mmol) was added. The suspension was heated at reflux overnight. While the suspension was still hot the insoluble material was filtered off and the resultant yellow solids were triturated with hot 1,4-dioxane to yield 2.79 g (5.86 mmol) of a yellow solid (90% yield, mp >200 °C). H^1 NMR (DMSO-d_6), δ 9.80 (H2′, 1H, s), 9.22 (H4′, 1H, d, J = 8 Hz), 9.20 (H6, 1H, d, J = 2 Hz), 9.02 (H6′, 1H, d, J = 7.0 Hz), 8.43 (H4, 1H, dd, J = 2 and 8 Hz), 8.26 (H3, 1H, d, J = 8 Hz), 8.22 (H5′, 1H, dd, J = 7 and 8 Hz), 8.20 (Ph, 2H, d, J = 8 Hz), 7.58 (Ph, 2H, d, J = 8 Hz), 5.0 (CH_2, 2H, t, J = 7 Hz), 3.43 (CH_2, 2H, t, J = 7 Hz). Anal. Calcd. for $C_{19}H_{17}O_3N_4I$: C, 47.91; H, 3.53; N, 11.76. Found: C, 47.85; H, 3.60; N, 11.77.

5-Carbamoyl- 1-methyl- 1′-(2-(4-nitrophenyl)ethyl)-2,3′-bipyridinium Diiodide (4-5a): A solution of 200 mg (0.420 mmol) of 4-4 in 3 mL of sulfolane and 1 mL of MeI (16 mmol) in a sealed tube was heated at 120 °C overnight. The mixture was cooled to 0 °C and then precipitated with 8 mL of EtOAc. After filtration the oily brown solid was dissolved in methanol, concentrated and coated onto 200 mg of octadecyl functionalized silica gel. This material was then added to the top of a reverse phase silica gel column and eluted with H_2O.[105] Removal of the water gave an orange oil which crystallized on standing. The solid was recrystallized from methanol and EtOAc to afford 39 mg (0.063 mmol) of yellow

crystals (15% yield, mp >200 °C). H^1 NMR (DMSO-d_6). δ 9.63 (H2′ or H6, 1H, s), 9.48 (H2′ or H6, 1H, s), 9.22 (H6′, 1H, d, J = 6 Hz), 9.03 (H4′, 1H, d, J = 8 Hz), 8.90 (H4, 1H, d, J = 7 Hz), 8.65 (NH, 1H, s), 8.39 (H5′, 1H, dd, J = 6 and 8 Hz), 8.30 (H3, 1H, d, J = 7 Hz), 8.27 (NH, 1H, s), 8.18 (Ph, 2H, d), 7.54 (Ph, 2H, d), 4.98 (CH_2, 2H, t, J = 7 Hz), 4.19 (CH_3, 3H, s), 3.45 (CH_2, 2H, t, J = 7 Hz). Anal. Calcd. for $C_{20}H_{20}O_3N_4I_2$: C, 38.85; H, 3.26; N, 9.06: Found: C, 38.78; H, 3.50; N, 8.99.

5- Carbamoyl- 1- methyl- 1′- (2- (4-nitrophenyl)ethyl)- 2,3′-bipyridinium Ditosylate (4-5b): A mixture of 4-4 (500 mg, 1.05 mmol), sulfolane (10 ml), and MeOTs (1.0 g, 5.4 mmol) was heated at 115 °C overnight. The solution was cooled to 0 °C and then precipitated with 10 mL of EtOAc. The solid was collected and washed 3 times with 20 mL portions of EtOAc to give 630 mg (0.891 mmol) of a white solid (85% yield, mp >220 °C). H^1 NMR (DMSO-d_6). δ 9.63 (H2′ or H6, 1H, s), 9.48 (H2′ or H6, 1H, s), 9.22 (H6′, 1H, d, J = 7 Hz), 9.03 (H4′ or H4, 1H, d, J = 9 Hz), 8.90 (H4′ or H4, 1H, d, J = 9 Hz), 8.65 (NH, 1H, s), 8.39 (H5′, 1H, dd, J = 7 and 9 Hz), 8.30 (H3, 1H, d, J = 9 Hz), 8.27 (NH, 1H, s), 8.18 (Ph, 2H, d, J = 7 Hz), 7.54 (Ph, 2H, d, J = 7 Hz), 7.50 (Ph, 4H, d, J = 7 Hz), 7.08 (Ph, 4H, d, J = 7 Hz), 4.98 (CH_2, 2H, t, J = 7 Hz), 4.19 (CH_3, 3H, s), 3.45 (CH_2, 2H, t, J = 7 Hz), 2.22 (CH_3, 6H, s). Anal. Calcd. for $C_{34}H_{34}N_4O_9S_2$: C, 57.76; H, 4.89; N, 7.93. Found: C, 58.20; H, 5.01; N, 8.07.

5-Carbamoyl-1-methyl-2,3′-bipyridinium Diperchlorate (4-6): A suspension of 1.0 g (1.4 mmol) of the tosylate of 4-5b, 30 mL of acetonitrile, and 0.14 g (1.7 mmol) of sodium acetate was heated at reflux for 48 h. The suspension was cooled to 0 °C and the insoluble NaOTs was collected. The filtrate was concentrated to a brown oil which was taken up in 20 mL of H_2O and 20 mL of EtOAc. The H_2O was then diluted with 80 mL of methanol and then mixed with 500 mg of octadecyl functionalized silica gel and concentrated to a powder. This material was placed on top of a reverse phase silica gel column and eluted with H_2O. Removal of the water gave a yellow oil. Addition of 30 mL of EtOAc caused the oil to solidify yielding 0.32 g (0.77 mmol) of a light brown solid (55% yield, mp >200 °C). H^1 NMR (DMSO-d_6). δ 9.62 (H6, 1H, s), 9.00 (H4, 1H, d, J = 8 Hz), 8.85 (H2′ and H6′, 2H, m), 8.65 (NH, 1H, s), 8.28 (H3, 1H, d, J = 8 Hz), 8.22 (NH, 1H, s), 8.18 (H4′, 1H, d, J = 8 Hz), 7.70 (H5′, 1H, dd, J = 5 and 8 Hz), 7.45 (Ph, 2H, d), 7.10 (Ph, 2H, d), 4.22 (CH_3, 3H, s), 2.29 (CH_3, 3H, s). This material was converted to its perchlorate salt on the addition of perchloric acid-EtOAc. Anal. Calcd for $C_{12}H_{13}Cl_2N_3O_9$: C, 34.80; H, 3.16; N, 10.14: Found: C, 34.53; H, 3.15; N, 10.00.

5-Carbamoyl-1′-(2-(4-nitrophenyl)ethyl)-2,3′-bipyridinium-1-oxide Tosylate (4-7): The iodide salt was first converted to the tosylate salt as follows. To a suspension of 4-4 (500 mg, 1.05 mmol) in 50 mL of acetonitrile was added

MeOTs (200 mg, 1.07 mmol). The suspension was stirred under a stream of nitrogen for two days. The precipitate was a white solid (546 mg, 1.05 mmol) which was suspended in 20 mL of sulfolane and 50% m-chloroperbenzoic acid (763 mg, 4.42 mmol). The reaction was stirred at room temperature for 3 days and the product was precipitated with 50 mL of 1:1 EtOAc:diethyl ether. The white precipitate was filtered and dried under vacuum to give 4-7, 320 mg (0.597 mmol, mp >220 °C, 57 % yield). H^1 NMR (DMSO-d_6): δ 9.72 (H2′, 1H, s), 9.08 (H4′ and H6′, 2H, m), 8.84 (H6, 1H, s), 8.22 (H5′, 1H, dd, J = 5 and 8 Hz), 8.19 (Ph and NH, 3H, d, J = 9 Hz), 7.95 (NH and H3 and H4, 3H, m), 7.57 (Ph, 2H, d, J = 8 Hz), 7.44 (Ph, 2H, d), 7.08 (Ph, 2H, d), 4.96 (CH_2, 2H, m), 3.50 (CH_2, 2H, m), 2.28 (CH_3, 3H, s). Anal. Calcd. for $C_{26}H_{24}N_4O_7S$: C, 58.20; H, 4.51; N, 10.44. Found: C, 58.24; H, 4.51; N, 10.38.

5-Carbamoyl-2,3′-bipyridine-1-oxide (4-8) by NPE Deprotection: To 50 mL of acetonitrile was added 4-7 (320 mg, 0.597 mmol) and dry sodium acetate (100 mg, 1.19 mmol). The solution was stirred at reflux for 24 h. The insoluble solids were removed and the filtrate was concentrated onto 2 g of silica gel and added to a column which was eluted with 70% EtOAc and 30% MeOH to give 80 mg (0.37 mmol) of a white solid (62% yield, mp >220°C). ^1H NMR (DMSO-d_6): δ 8.96 (H2′, 1H, d, J = 2 Hz), 8.60 (H6′, 1H, dd, J = 2 and 5 Hz), 8.52 (H6, 1H, s), 8.27 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 7.71 (H4, 1H, d, J = 9 Hz), 7.61 (H3, 1H, d, J = 9 Hz), 7.48 (H5′, 1H, dd, J = 5

and 9 Hz). Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.23; H, 4.22; N, 19.55.

5-Carbamoyl-1'-methyl-2,3'-bipyridinium-1-oxide Tosylate (4-9): To trifluoroacetic acid (10 mL) was added 4-2 (750 mg, 1.95 mmol) and urea-H_2O_2 complex (320 mg, 3.40 mmol)). The solution was stirred overnight at room temperature with an additional 100 mg (1.06 mmol) addition of the urea-H_2O_2 complex after the first 2 h. The mixture was diluted with 10 mL of water and the product was precipitated with isopropyl alcohol to give after filtration 673 mg (1.68 mmol) of a yellow solid (86% yield, mp >200 °C). ^{1}H NMR (DMSO-d_6): δ 9.60 (H2', 1H, s), 9.07 (H4' and H6', 2H, m), 8.85 (H6, 1H, s), 8.38 (NH, 1H, s), 8.25 (H5', 1H, dd, J = 6 and 9 Hz), 8.03 (H4, 1H, d, J = 9 Hz), 7.95 (NH and H3, 2H, bd), 7.48 (Ph, 2H, d, J = 9 Hz), 7.11 (Ph, 2H, d, J = 9 Hz), 4.42 (CH_3, 3H, s), 2.26 (CH_3, 3H, s). Anal. Calcd. for $C_{19}H_{19}N_3O_5S.0.5H_2O$: C, 55.60; H, 4.91; N, 10.24. Found: C, 55.22; H, 4.59; N, 10.47.

5-Carbamoyl-2,3'-bipyridine-1-oxide (4-8) by Demethylation: To 4-9 (340 mg, 0.847 mmol) dissolved in 20 mL of DMF was added KI (280 mg, 1.68 mmol). The mixture was heated at 120 °C for 36 h and then concentrated to a brown oil and dissolved in 40 mL of MeOH. The insoluble material was removed and the filtrate was concentrated onto 2 g of silica gel and added to the top of a silica gel column which then was eluted with 80% EtOAc and 20% MeOH to yield 100 mg (0.465 mmol) of a white solid. (55% yield, mp >220°C).

1'-Methyl-2,3'-bipyridinium-1-oxide Tosylate (4-11): To 20 mL of CH_2Cl_2 was added 2,3'-bipyridine (500 mg, 3.20 mmol) and MeOTs (600 mg, 3.22 mmol). The solution was stirred at room temperature for 24 h. The solvent was concentrated to yield 1.10 grams (3.20 mmol) of a slightly yellow oil which was added to 30 mL of $CHCl_3$ and 50% of m-chloroperbenzoic acid (2.21 g, 12.8 mmol). The solution was stirred at room temperature for 48 h. The $CHCl_3$ was washed once with 30 mL of water. The aqueous layer was separated and concentrated to 800 mg (2.23 mmol) of yellow oil; this crude material was used directly for the deprotection step. ^1H NMR (DMSO-d_6): δ 9.58 (H2', 1H, s), 9.05 (H4' and H6', 2H, m), 8.50 (H6, 1H, d, J = 5 Hz), 8.24 (H5', 1H, dd, J = 5 and 8 Hz), 7.85 (H4, 1H, t, J = 8 Hz), 7.60 (H3 and H5, 2H, m), 7.48 (Ph, 2H, d, J = 8 Hz), 7.05 (Ph, 2H, d, J = 8 Hz), 4.40 (CH_3, 3H, s), 2.25 (CH_3, 3H, s).

2,3'-Bipyridine-1-oxide (4-10) by Deprotection: Crude 4-11 (300 mg, 0.840 mmol) was dissolved in 10 mL of DMF and KI (280 mg, 1.68 mmol) was added. The reaction was heated at 120 °C for 24 h and then concentrated to a brown oil and dissolved in MeOH. The insoluble material was removed and the filtrate was concentrated onto 1 g of silica gel and added to the top of a silica gel column which then was eluted with 90% EtOAc and 10% MeOH to yield 59 mg (0.34 mmol) of a white solid (mp 135-137 °C, 40% yield). ^1H NMR (DMSO-d_6) δ 8.95 (H2', 1H, d, J = 2 Hz), 8.63 (H6', 1H, dd, J = 2 and 5 Hz), 8.37 (H6, 1H, dd,

J = 2 and 6 Hz), 8.27 (H4', 1H, dt, J = 2, 2 and 9 Hz), 7.73 (H4, 1H, dd, J = 2 and 8 Hz), 7.52 (H5', 1H, dd, J = 5 and 9 Hz), 7.44 (H3 and H5, 2H, m). Anal. Calcd. for $C_{10}H_7N_2O$: C, 69.75; H, 4.63; N, 16.27: Found C, 70.03; H, 4.69; N, 16.29.

6-Chloronicotinamide-1-oxide: 6-Chloronicotinamide (800 mg, 5.75 mmol) and urea-H_2O_2 complex (930 mg, 9.89 mmol)) were dissolved in 10 mL of triflouroacetic acid. The solution was stirred overnight at room temperature under nitrogen with the addition of 300 mg (3.19 mmol) urea-H_2O_2 after each of the first two hours. The reaction was diluted with 50 mL of H_2O and 50 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted 3 times with 50 mL of ethyl acetate. The extracts were combined, dried, and concentrated to a clear liquid. Column chromotography with Kieselgel and 80% ethyl acetate/20% methanol gave 850 mg (4.93 mmol) of an off-white solid (86% yield, mp 124-128 °C). ^{1}H NMR (DMSO-d_6) δ 8.80 (H2, 1H, d, J = 2 Hz), 8.24 (NH, 1H, s), 7.88 (H3, 1H, d, J = 9 Hz), 7.82 (NH, 1H, s), 7.70 (H4, 1H, dd, J = 2 and 9 Hz). Anal. Calcd. for $C_5H_5N_2O_2Cl$ .1/3 H_2O: C, 40.35: H, 3.20; N, 16.69: Found C, 40.50; H, 2.91; N, 15.24.

Pd-Catalyzed Coupling to Prepare 5-Carbamoyl-2,3'-Bipyridine-1-oxide (4-8): 6-Chloronicotinamide-1-oxide (175 mg, 1.01 mmol), diethyl(3-pyridyl)borane (150 mg, 1.01 mmol), and tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.173 mmol) were added to 20 mL of degassed THF. The suspension was stirred under nitrogen for 5 min and then K_2CO_3 (280 mg, 2.03

mmol) in 10 mL of water was added. The solution was heated at reflux for 24 h and then cooled to 0 °C and the black insoluble solid was removed by filtration. The reaction was diluted with 30 mL of water and 30 mL EtOAc. The aqueous layer was separated and concentrated to a yellow solid which was triturated with hot MeOH. Solids were collected and the filtrate was concentrated to a white solid which was recrystallized with 95% EtOH and EtOAc to give 160 mg (0.743 mmol) of a white solid (73% yield, mp> 220 °C). The ^{1}H NMR (DMSO-d_6) was the same as that above.

Pd-Catalyzed Coupling to Prepare 2,3'-Bipyridine-1-oxide (4-10): 2-Bromopyridine-1-oxide hydrochloride (500 mg, 2.38 mmol), diethyl(3-pyridyl)borane (350 mg, 2.38 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.260 mmol) were added to 30 mL of degassed THF. The suspension was stirred under nitrogen for 5 min and then K_2CO_3 (1.65 g, 12.0 mmol) in 15 mL of water was added. The solution was heated at reflux for 48 h and then cooled to 0 °C and the catalyst was collected. To the filtrate was added 30 mL of EtOAc and 30 mL water. The aqueous layer was separated and concentrated to a white solid which was triturated with 20 mL of MeOH; the solid material was collected. The methanolic layer was concentrated to 280 mg (1.63 mmol) of a white solid (mp 136-137 °C, 68% yield). The ^{1}H NMR (DMSO-d_6) was the same as that above.

3-Tributylstannyl-2,3'-bipyridine (5-13): 2-Bromo-3-(tributyl-stannyl)pyridine (1.00 g, 2.24 mmol), diethyl(3-

pyridyl)borane (658 mg, 4.47 mmol), and tetrakis(triphenyl phosphine)palladium(0) (129 mg, 0.112 mmol) were dissolved in 20 mL of degassed THF under N_2. The solution was stirred at room temperature for 5 min and then $NaHCO_3$ (564 mg, 6.71 mmol) dissolved in 10 mL of degassed H_2O was added. The solution was stirred at reflux for 3 h and then cooled to room temperature. The mixture was diluted with 30 mL of EtOAc and the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel 60 and 100% EtOAc gave 911 mg of a clear oil which was contaminated with a small amount of $Ph_3P=O$. The $Ph_3P=O$ crystallized on standing and was removed by filtration with hexanes to give 860 mg (1.93 mmol, 86 % yield) of a clear oil. ^1H NMR ($CDCl_3$) δ 8.71 (H2, 1H, d, J = 2 Hz), 8.65 (H6′, 1H, dd, J = 1 and 5 Hz), 8.61 (H6, 1H, dd, J = 2 and 5 Hz), 7.87 (H4 and H4′, 2H, m), 7.36 (H5′, 1H, dd, J = 5 and 9 Hz), 7.24 (H5, 1H, dd, J = 5 and 9 Hz), 0.87-1.40 (27H, m). Anal. Calcd. for $C_{22}H_{34}N_2Sn$: C, 59.35; H, 7.70; N, 6.29. Found: C, 59.58; H, 7.70; N, 5.98.

3-Chloro-2,3′-bipyridine (5-10): Diethyl(3-pyridyl)borane (690 mg, 4.69 mmol), 2,3-dichloropyridine (1.41 g, 9.52 mmol) and tetrakis(triphenylphosphine)palladium(0) (578 mg, 0.500 mmol) were placed in degassed THF (25 mL) under N_2. The mixture was stirred for 15 min at room temperature and then K_2CO_3 (1.50 g, 10.9 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C. After the insoluble catalyst was filtered off, the

filtrate was diluted with 25 mL of EtOAc. The organic layer was separated, washed with 20 mL of brine and then extracted twice with 10 mL portions of 2 M HCl. The two acid washes were combined, neutralized with sodium carbonate, and then extracted twice with 20 mL portions of EtOAc. The organic extracts were combined, dried, and concentrated to an orange oil. Column chromatography with Kieselgel and 1:1 EtOAc:hexanes gave 823 mg (4.32 mmol) of a light yellow solid (mp 66-69 °C, 92% total yield). ^{1}H NMR ($CDCL_3$) δ 9.01 (H2′, 1H, dd, J = 1 and 2 Hz), 8.68 (H6′, 1H, dd, J = 2 and 5 Hz), 8.63 (H6, 1H, dd, J = 2 and 5 Hz), 8.08 (H4′, 1H, dt, J = 2, 2 and 8 Hz), 7.84 (H4, 1H, dd, J = 2 and 8 Hz), 7.42 (H5′, 1H, ddd, J = 1, 5 and 8 Hz), 7.29 (H5, 1H, dd, J = 5 and 8 Hz). Anal. Calcd. for $C_{10}H_7N_2Cl$: C, 63.00; H, 3.70; N, 14.70. Found: C, 62.72; H, 3.61; N, 14.49.

3-Amino-2,3′-bipyridine (5-15): Diethyl(3-pyridyl)borane (1.14 g, 7.78 mmol), 3-amino-2-chloropyridine (1.00 g, 7.78 mmol) and tetrakis(triphenylphosphine)palladium(0) (578 mg, 0.500 mmol) were placed in degassed THF (25 mL) under N_2. The mixture was stirred for 10 min at room temperature and then potassium carbonate (5.37 g, 38.9 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C. After the insoluble catalyst was filtered off, the filtrate was diluted with 25 mL of EtOAc. The organic phase was separated, washed with 20 mL of brine, and then extracted twice with 10 mL portions of 2 M HCL. The acid

extracts were combined, neutralized with sodium carbonate and extracted twice with 20 mL portions of ethyl acetate. The extracts were combined, dried and concentrated to a red oil. Column chromatography with Kieselgel 60 and 100% ethyl acetate gave 580 mg (3.39 mmol) of slightly red crystals (mp 70-74 °C, 44% yield). ^{1}H NMR ($CDCl_3$) δ 8.98 (H2′, d, 1H, J = 2 Hz), 8.65 (H6′, dd, 1H, J = 2 and 6 Hz), 8.15 (H6, dd, 1H, J = 2 and 6 Hz), 8.09 (H4′, dt, 1H, J = 2, 2 and 9 Hz), 7.45 (H5′, dd, 1H, J = 6 and 9 Hz), 7.12 (H4 and H5, m, 2H), 3.2 (NH_2, b, 2H). Anal. Calcd. for $C_{10}H_9N_3$ 1/8 H_2O: C, 69.24; H, 5.38; N, 24.22. Found: C, 69.48; H, 5.31; N, 24.32.

3-Bromo-2,3′-bipyridine (5-14): A cooled (-10 °C) suspension of 3-amino-2,3′-bipyridine (5-15) (365 mg, 1.55 mmol) in 48% HBr (1.5 mL) was stirred for 0.5 h and Br_2 (0.25 mL, 4.33 mmol) was added. Keeping the reaction below 0 °C, $NaNO_2$ (300 mg, 4.33 mmol) in H_2O (0.4 mL) was added dropwise. After stirring for 0.5 h, NaOH (800 mg, 20.0 mmol) in H_2O (1 mL) was added dropwise making sure the temperature did not exceed 0 °C. The basic aqueous phase was extracted 3x with 20 mL of diethyl ether and the extracts were combined, dried, and concentrated to give 200 mg (0.851 mmol) of an off-white solid (mp 75-77 °C, 55% yield). ^{1}H NMR ($CDCl_3$) δ 8.88 (H2′, 1H, d, J = 2 Hz), 8.58 (H6 and H6′, 2H, m), 7.93 (H4 and H4′, 2H, m), 7.32 (H5′, 1H, ddd, J = 1, 5 and 9 Hz), 7.12 (H5, 1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{10}H_7N_2Br$: C, 51.09; H, 3.00; N, 11.92. Found: C, 51.54; H, 2.96; N, 11.76.

4-Chloro-2,3′-bipyridine (5-5): 2,4-Dichloropyridine[114] (3.45 g, 23.3 mmol), diethyl(3-pyridyl)borane (3.40 g, 23.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (1.30 g, 11.3 mmol) in degassed THF (80 mL) were stirred at room temperature under N_2. After 5 min, potassium carbonate (6.44 g, 46.6 mmol) in degassed H_2O (40 mL) was added and the mixture was heated at reflux for 3 h. The mixture was diluted with 50 mL of EtOAc and the organic layer was dried and concentrated to a red oil. Column chromatography with Kieselgel 60 and 100% EtOAc gave 2.50 g (13.1 mmol) of a slightly yellow oil which crystallized on standing (mp 49-51 °C, 57% yield). ^{1}H NMR ($CDCl_3$) δ 9.33 (H2′, 1H, d, J = 2 Hz), 9.03 (H6, 1H, d, J = 6 Hz), 8.76 (H6′, 1H, dd, J = 2 and 5 Hz), 8.49 (H3, 1H, d, J = 2 Hz), 8.41 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 8.03 (H5, 1H, dd, J = 2 and 6 Hz), 7.49 (H5′, 1H, ddd, J = 2, 5 and 9 Hz). Anal. Calcd. for $C_{10}H_7N_2Cl$: C, 63.00; H, 3.70; N, 14.70. Found: C, 63.05; H, 3.70; N, 14.59.

4-Chloro-2,3′-bipyridine-1′-oxide (5-6): To a $CHCl_3$ (50 mL) solution of 4-chloro-2,3′-bipyridine (5-5) (2.50 g, 13.1 mmol) was added 57-80% MCPBA (2.83 g, 16.4 mmol). The solution was stirred at room temperature for 24 h and was then washed with 10 mL of sat. sodium sulfite, dried, and concentrated to a slightly yellow solid. Column chromatography with Kieselgel and 90/10 EtOAc/MeOH gave 1.67 g (8.08 mmol) of a white solid (mp 109-112 °C, 62% yield). ^{1}H NMR ($CDCl_3$) δ 9.05 (H2′ and H6, 2H, m), 8.45 (H3, 1H, d, J = 2 Hz), 8.34 (H4′, 1H, dt, J = 2,

2 and 8 Hz), 8.10 (H6′, 1H, dd, J = 2 and 6 Hz), 7.96 (H5, 1H, dd, J = 2 and 6 Hz), 7.46 (H5′, 1H, dd, J = 6 and 8 Hz). Anal. Calcd. for $C_{10}H_7N_2OCl$ .1/2 H_2O: C, 55.69; H, 3.74; N, 12.99. Found: C, 55.76; H, 3.67; N, 13.33.

2′,4-Dichloro-2,3′-bipyridine (5-4): A suspension of 4-chloro-2,3′-bipyridine-1′-oxide (5-6) (500 mg, 2.42 mmol) and acetic anhydride (20 mL) was heated at reflux for 12 h. The mixture was concentrated to a brown oil, dissolved in 15 mL of MeOH, decolorized with charcoal, and filtered through a bed of Celite. The filtrate was concentrated to a yellow solid which was washed with 20 mL of diethyl ether to give 240 mg (1.16 mmol, 48% yield) of a slightly yellow solid of the pyridone. The solid was suspended in $POCl_3$ (5 mL) and DMF (1 mL) and heated at reflux for 18 h. The reaction was concentrated to a brown oil and sodium carbonate/ice/H_2O was added until the aqueous phase was slightly basic to pH paper. The aqueous phase was extracted with 50 mL of EtOAc and the organic phase was dried and concentrated to a brown oil. Column chromatography with Kieselgel and 100% EtOAc gave 80 mg (0.36 mmol) of a yellow solid (mp 156-159 °C, 32% yield). ^1H NMR ($CDCl_3$) δ 8.68 (H6′, 1H, d, J = 6 Hz), 8.51 (H6, 1H, dd, J = 2 and 6 Hz), 8.02 (H4′, 1H, dd, J = 2 and 8 Hz), 7.92 (H3, 1H, d, J = 2 Hz), 7.51 (H5 and H5′, 2H, m). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.71; H, 2.62; N, 12.40.

3,4′-Bipyridine-1′-oxide (5-7): 4-Chloropyridine-N-oxide (1.40 g, 10.8 mmol), diethyl(3-pyridyl)borane (1.59 g, 10.8 mmol), tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.430 mmol) in degassed THF (30 mL) were stirred for 5 min at room temperature under N_2. Potassium carbonate (2.98 g, 21.6 mmol), dissolved in degassed H_2O (15 mL), was added and the mixture was heated at reflux. After 48 h, the mixture was concentrated and MeOH (50 mL) was added. The insoluble K_2CO_3 was filtered off and the filtrate was concentrated onto approx. 5 g of Kieselgel. Column chromatography with 80/20 EtOAc/MeOH gave 1.40 g (8.13 mmol) of an off-white solid (mp 125-127 °C, 75% yield). ^{1}H NMR (DMSO-d_6) δ 8.82 (H2′, 1H, d, J = 2 Hz), 8.61 (H6′, 1H, dd, J = 2 and 5 Hz), 8.14 (H2, 2H, d, J = 8 Hz), 8.02 (H4′, 1H, dt, J = 2, 2 and 8 Hz), 7.65 (H3, 2H, d, J = 9 Hz), 7.38 (H5′, 1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{10}H_7N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.35; H, 4.67; N, 16.09.

2′-Chloro-3,4′-bipyridine (5-8): To a cooled (0 °C) suspension of 3,4′-bipyridine-1′-oxide (5-7) (700 mg, 4.07 mmol) in CH_2Cl_2 (5 mL) under N_2 was added $POCl_3$ (2 mL). To this slurry additional $POCl_3$ (2 mL) and $(i\text{-}Pr)_2NH$ (2 mL) were added concomitantly over 2 h. The mixture became brown and homogeneous. It was stirred for 1 h while warming to room temperature and was then concentrated to a brown oil. To the oil, Na_2CO_3/ice/H_2O was added until the aqueous phase was slightly basic to pH paper. The aqueous phase was extracted

with 30 mL of EtOAc and the organic phase was dried and concentrated to a brown solid. Column chromatography with Kieselgel and 100% EtOAc gave 320 mg (1.68 mmol) of a yellow solid (mp 114-115 °C, 41% yield). ^{1}H NMR ($CDCl_3$) δ 8.89 (H2′, 1H, d, J = 2 Hz), 8.72 (H6′, 1H, dd, J = 2 and 5 Hz), 8.50 (H6, 1H, d, J = 6 Hz), 7.92 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 7.58 (H3, 1H, d, J = 1 Hz), 7.46 (H5 and H5′, 2H, m). Anal. Calcd. for $C_{10}H_7N_2O$: C, 63.00; H, 3.70; N, 14.70. Found: C, 62.96; H, 3.65; N, 14.59.

2′-Tributylstannyl-3,4′-bipyridine (5-9): 2′-Chloro-3,4′-bipyridine (5-8) (100 mg, 0.522 mmol), freshly distilled THF (10 mL), and Mg (25 mg, 1.04 mmol) were stirred at room temperature under N_2. The reaction was initiated with two drops of 1,2-dibromoethane and then tributyltin chloride (0.500 mL, 1.84 mmol) was added dropwise. After the addition, the mixture was heated at reflux for 4 h and then cooled to room temperature. The reaction was diluted with 30 mL of satd. NH_4Cl and 30 mL of diethyl ether. The organic phase was separated, dried, and concentrated to a yellow oil. Column chromatography with Kieselgel and 60/40 hexanes/EtOAc gave 80 mg (0.18 mmol) of a clear oil (34% yield). ^{1}H NMR ($CDCl_3$) δ 8.86 (H2′, 1H, d, J = 2 Hz), 8.84 (H6, 1H, dd, J = 1 and 6 Hz), 8.66 (H6′, 1H, dd, J = 2 and 6 Hz), 7.91 (H4′, 1H, dt, J = 2, 2 and 9 Hz), 7.59 (H3, 1H, dd with Sn side bands, J = 1 and 2 Hz), 7.43 (H5′, 1H, ddd, J = 1, 6 and 9 Hz), 7.33 (H5, 1H, dd, J = 2 and 6 Hz), 0.87-1.40 (27H, m). Anal. Calcd. for

$C_{22}H_{34}N_2Sn$: C, 59.35; H, 7.70; N, 6.29. Found: C, 59.67; H, 7.74; N, 6.00.

3,2′:3′,3"-Terpyridine (5-13): Diethyl(3-pyridyl)borane (368 mg, 2.50 mmol), 3-chloro-2,3′-bipyridine[129] (448 mg, 2.35 mmol), and $Pd(PPh_3)_4$ (578 mg, 0.500 mmol) were placed in degassed THF (25 mL) under N_2. The mixture was stirred for 10 min at room temperature, and potassium carbonate (685 mg, 4.96 mmol) in degassed H_2O (10 mL) was added. The mixture was heated at reflux for 72 h and then cooled to 0 °C with ice. The insoluble catalyst was filtered off and the filtrate was diluted with 25 mL of EtOAc. The organic phase was separated, washed with 20 mL of brine, and extracted twice with 10 mL portions of 2 M HCL. The acid extracts were combined, neutralized with sodium carbonate, and extracted twice with 20 mL portions of EtOAc. The organic extracts were combined, dried, and concentrated to a yellow oil. Column chromatography with Kieselgel and 90/10 EtOAc/MeOH gave 348 mg (1.49 mmol, 62% yield) of a clear oil. ^1H NMR ($CDCl_3$) δ 8.78 (H6′, 1H, d, J = 6 Hz), 8.52 (H2, H2′′, H6′′ and H6, 4H, m), 7.80 (H4′, d, 1H, J = 8 Hz), 7.70 (H4, dd, 1H, J = 2 and 9 Hz), 7.45 (H5′ and H4′′, m, 2H), 7.23 (H5′ and H5′′, m, 4H). A 100 mg portion of this material was converted to the trihydrochloride salt by dissolving it in 5 mL of EtOAc and adding HCl-ether dropwise. The solid was collected and dried in vacuo to give a white solid. Anal. Calcd. for $C_{15}H_{11}N_3$ .3HCl: C, 52.42; H, 12.23; N, 4.40. Found: C, 52.29; H, 4.20; N, 12.28.

3,2′: 3′,2′′: 4′′,3′′′-Quaterpyridine (5-1): 2′,4-Dichloro-2,3′-bipyridine (5-4) (80 mg, 0.36 mmol), diethyl(3-pyridyl) borane (131 mg, 0.889 mmol), and tetrakis(triphenylphosphine) palladium(0) (41 mg, 0.036 mmol) in degassed THF (80 mL) were stirred at room temperature under N_2. After 5 min, sodium bicarbonate (119 mg, 1.42 mmol) in degassed H_2O (10 mL) was added, and the mixture was heated at reflux for 24 h. The mixture was diluted with 50 mL of EtOAc, and the organic layer was separated, dried and concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 70 mg (0.23 mmol, 64 % yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.82 (H6′, 1H, dd, J = 2 and 5 Hz), 8.76 (H6′′, 1H, dd, J = 1 and 6 Hz), 8.64 (H6′′′, 1H, dd, J = 2 and 6 Hz), 8.56 (H2 and H2′′′ and H6, 3H, m), 8.12 (H4′, 1H, dd, J = 2 and 9 Hz), 7.87 (H4, 1H, dt, J = 2, 2 and 9 Hz), 7.61 (H4′′′, 1H, dt, J = 2, 2 and 9 Hz), 7.48 (H5′, 1H, dd, J = 5 and 9 Hz), 7.43 (H5′′, 1H, dd, J = 2 and 6 Hz), 7.35 (H5′′′, 1H, ddd, J = 2, 6 and 9 Hz), 7.31 (H5, 1H, ddd, J = 2, 6 and 9 Hz), 7.23 (H3′′, 1H, dd, J = 1 and 2 Hz). Anal. Calcd. for $C_{20}H_{14}N_4$ .1/4 H_2O: C, 76.26; H, 4.64; N, 17.80. Found: C, 76.40; H, 5.03; N, 17.82.

3,2′:3′,4′′:2′′,3′′′-Quaterpyridine (Nemertelline, 5-3): A degassed solution of 4-chloro-2,3′-bipyridine (5-5) (132 mg, 0.694 mmol) in toluene and tetrakis(triphenylphosphine) palladium(0) (80 mg, 0.069 mmol) were stirred at room temperature under N_2 for 15 min. 3′-Tributylstannyl-2′,3-

bipyridine (5-13) (618 mg, 1.39 mmol) was added and the solution was heated at reflux for 96 h. The mixture was cooled to room temperature, filtered through a bed of Celite to remove black catalyst and concentrated to an oil. Column chromatography with Kieselgel 60 and 80/20 EtOAc/MeOH gave 140 mg (0.451 mmol, 70% yield) of a clear oil. The oil, dissolved in warm diethyl ether, slowly crystallized with scratching (mp 154-156 °C). ^{1}H NMR ($CDCl_3$) δ 9.00 (H2′, 1H, dd, J = 1 and 3 Hz), 8.84 (H6′, 1H, dd, J = 2 and 5 Hz), 8.67 (H6′′, 1H, dd, J = 1 and 6 Hz), 8.65 (H6′′′, 1H, dd, J = 2 and 5 Hz), 8.62 (H2, 1H, dd, J = 1 and 3 Hz), 8.57 (H6, 1H, dd, J = 2 and 5 Hz), 8.19 (H4′′′, 1H, dt, J = 2, 2 and 9 Hz), 7.85 (H4′, 1H, dd, J = 2 and 9 Hz), 7.78 (H4, 1H, dt, J = 2, 2 and 9 Hz), 7.56 (H3′′, 1H, dd, J = 1 and 2 Hz), 7.49 (H5′, 1H, dd, J = 5 and 9 Hz), 7.39 (H5′′′, 1H, ddd, J = 1, 5 and 9 Hz), 7.28 (H5, 1H, ddd, J = 1, 5 and 9 Hz), 7.14 (H5′′, 1H, dd, J = 2 and 5 Hz) . Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.34; H, 4.56; N, 18.13.

Crystal Structure of Nemertelline (5-2)[1]: Colorless crystals of nemertene were grown in $CHCl_3$. They are monoclinic, space group Cc, M_r=310.35, a=18.684(3) Å, b=8.009(1) Å, c=11.393(2) Å, β=113.92(1)°, V=1558.4(4) Å^3, Z=4, $D_{calc.}$=1.323 g cm^{-3}, Mo Kα(λ=0.71073 Å), T=298 K. The structure was solved by the direct method and refined in *SHELZTL plus*

[1]Crystal Structure work kindly done by Dr. Kalil A. Abboud.

using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the positions of the hydrogen atoms were calculated in ideal positions and their isotropic thermal parameters were fixed. The systematic absences could not differenciate between space groups C2, Cc and C2/c. All three

Table 8-1. Fractional Coordinates and Equivalent Isotropic[a] Thermal Parameters ($Å^2$) for the Carbon and Nitrogen Atoms of 5-3.

Atom	x	y	z	U
N1	0.03265	0.5451(3)	0.2134	0.0538(9)
C2	-0.0329(2)	0.4550(3)	0.1760(3)	0.0448(9)
C3	-0.0623(2)	0.3581(3)	0.0662(3)	0.0386(8)
C4	-0.0209(2)	0.3587(4)	-0.0112(3)	0.048(1)
C5	0.0472(2)	0.4497(4)	0.0262(3)	0.057(1)
C6	0.0718(2)	0.5397(4)	0.1383(3)	0.055(1)
N11	-0.1847(2)	0.2744(3)	-0.0954(3)	0.0489(8)
C12	-0.1360(2)	0.2615(3)	0.0290(3)	0.0380(8)
C13	-0.1543(2)	0.1664(3)	0.1157(3)	0.0389(8)
C14	-0.2273(2)	0.0876(4)	0.0704(3)	0.051(1)
C15	-0.2774(2)	0.1035(4)	-0.0575(3)	0.058(1)
C16	-0.2537(2)	0.1966(4)	-0.1351(3)	0.056(1)
N21	0.0030(2)	0.0809(3)	0.5077(3)	0.0427(8)
C22	0.0259(2)	0.0519(3)	0.4119(3)	0.0341(8)
C23	-0.0236(2)	0.0808(3)	0.2837(3)	0.0362(8)
C24	-0.0993(2)	0.1389(3)	0.2523(3)	0.0365(8)
C25	-0.1227(2)	0.1666(3)	0.3516(3)	0.0438(9)
C26	-0.0691(2)	0.1370(3)	0.4758(3)	0.046(1)
N31	0.1992(2)	-0.1612(3)	0.3904(3)	0.0575(9)
C32	0.1277(2)	-0.1014(3)	0.3633(3)	0.0452(9)
C33	0.1065(2)	-0.0129(3)	0.4490(3)	0.0357(8)
C34	0.1641(2)	0.0118(4)	0.5717(3)	0.047(1)
C35	0.2382(2)	-0.0509(4)	0.6018(3)	0.053(1)
C36	0.2529(2)	-0.1336(4)	0.5092(3)	0.054(1)

[a]For anisotropic atoms, the U value is U_{eq}, calculated as $U = 1/3 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* A_{ij}$ where A_{ij} is the dot product of the i^{th} and j^{th} direct space unit cell vectors.

Table 8-2. Bond Lengths (Å) and Angles (°) for the Carbon and Nitrogen Atoms of 5-3.

1	2	3	1-2	1-2-3
C2	N1	C6	1.334(3)	116.7(2)
C6	N1		1.333(4)	
C3	C2	N1	1.382(4)	124.7(3)
C4	C3	C12	1.389(6)	120.8(3)
C4	C3	C2		117.0(3)
C12	C3	C2	1.484(4)	122.2(3)
C5	C4	C3	1.375(5)	119.2(3)
C6	C5	C4	1.373(5)	119.0(4)
N1	C6	C5		123.4(3)
C12	N11	C16	1.342(4)	118.1(3)
C16	N11		1.334(5)	
C13	C12	C3	1.395(5)	123.2(2)
C13	C12	N11		122.3(3)
C3	C12	N11		114.5(3)
C14	C13	C24	1.397(5)	118.4(3)
C14	C13	C12		117.8(3)
C24	C13	C12	1.493(4)	123.8(3)
C15	C14	C13	1.382(4)	119.4(3)
C16	C15	C14	1.361(6)	118.4(3)
N11	C16	C15		124.0(3)
C22	N21	C26	1.344(5)	117.3(3)
C26	N21		1.324(5)	
C23	C22	C33	1.395(4)	121.4(3)
C23	C22	N21		121.9(3)
C33	C22	N21	1.483(4)	116.7(2)
C24	C23	C22	1.391(5)	119.8(3)
C25	C24	C13	1.387(5)	121.0(3)
C25	C24	C23		117.9(3)
C13	C24	C23		121.1(3)
C26	C25	C24	1.382(4)	118.0(3)
N21	C26	C25		125.0(4)
C32	N31	C36	1.332(5)	116.5(3)
C36	N31		1.336(4)	
C33	C32	N31	1.388(5)	124.5(3)
C34	C33	C22	1.390(4)	121.3(3)
C34	C33	C32		117.0(3)
C22	C33	C32		121.7(2)
C35	C34	C33	1.379(5)	119.2(3)
C36	C35	C34	1.364(6)	118.8(3)
N31	C36	C35		124.0(3)

space groups were tried in the structure solution process but only Cc gave a solution. All refinements were carried out in space group Cc. In the final cycle of refinement 215 parameters and 1597 reflections [with $I>2\delta(I)$] gave R and *w*R of 0.0373 and 0.0432, respectively.

2,4′-Bipyridine-di-N-oxide (6-3): To a solution of 2,4′-bipyridine (1.60 g, 10.2 mmol) in $CHCl_3$ (50 mL) was added 57-80% MCPBA (6.63 g, 38.4 mmol). The complete solution was stirred overnight at room temperature and then washed twice with 25 mL of H_2O. The aqueous extracts were combined and concentrated to give 1.40 g of a white solid. The solid was washed with 25 mL of diethyl ether and then recrystallized with isopropanol/H_2O. The result was 1.04 g (5.53 mmol) of a white solid (mp> 200 °C, 54% yield). ^1H NMR (DMSO-d_6) δ 8.38 (H6′, 1H, dd, J = 2 and 5 Hz), 8.32 (H2, 2H, d, J = 7 Hz), 8.05 (H3, 2H, d, J = 7 Hz), 7.81 (H4′, 1H, dd, J = 5 and 6 Hz), 7.54 (H3′ and H5′, 2H, m).

2′,6-Dichloro-2,4′-bipyridine (6-4) and 2′,4-dichloro-2,4′-bipyridine (6-5): A suspension of 2,4′-bipyridine-di-N-oxide (1.00 g, 5.31 mmol) in acetic anhydride (30 mL) was heated at reflux for 8 h. The mixture was concentrated to a brown oil and dissolved in 50 mL of MeOH which was decolorized with charcoal and filtered through a bed of Celite. The filtrate was concentrated to a brown solid which was washed with 50 mL of diethyl ether to give 600 mg of the dipyridone.

The material was suspended in $POCl_3$ (15 mL)/DMF (2 mL) and heated at reflux for 8 h under N_2. The mixture was concentrated to a brown oil and sodium carbonate/ice/H_2O was added until the aqueous phase was basic to pH paper. The aqueous phase was extracted with 50 mL of $CHCl_3$ and the organic phase was dried and concentrated to a brown oil. Column chromatography with Kieselgel and 90/10 hexanes/EtOAc gave 400 mg (1.78 mmol) of a yellow solid (145-147 °C, 33% yield). ^1H NMR ($CDCl_3$) δ 8.50 (H6′, 1H, dd, J = 1 and 5 Hz), 7.96 (H3′, 1H, dd, J = 1 and 2 Hz), 7.81 (H4 and H5′, 2H, m), 7.72 (H3, 1H, dd, J = 1 and 8 Hz), 7.42 (H5, 1H, dd, J = 1 and 8Hz). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.52; H, 2.44; N, 12.28.

In addition, 50 mg (0.22 mmol, 4%) of slightly less polar 6-5 as a yellow solid (mp 116-120 °C) was isolated from the column in an early fraction. ^1H NMR ($CDCl_3$) δ 8.64 (H6 or H6′, 1H, d, J = 5 Hz), 8.51 (H6 or H6′, 1H, d, J = 5 Hz), 7.95 (H3, 1H, d, J = 1 Hz), 7.79 (H3′ and H5, 2H, m), 7.39 (H5′, 1H, dd, J = 2 and 5 Hz). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.65; H, 2.37; N, 12.39.

2,2′:4′,2″:6″,2‴-Quaterpyridine (6-1): A solution of 2,6′-dichloro-2,4′-bipyridine (6-4) (100 mg, 0.444 mmol) and tetrakis(triphenylphosphine) palladium(0) (51 mg, 0.044 mmol) in degassed toluene was stirred at reflux for 15 min under N_2. 2-(Tributylstannyl)pyridine (654 mg, 1.78 mmol) was added in three equal portions over 1 h. The reaction was stirred at

reflux for 48 h and then concentrated to an oil. Column chromatography with alumina and 80/20 EtOAc/hexanes gave 95 mg of a white solid. The product was washed with 30 mL of diethyl ether to give 78 mg (0.25 mmol, 139-141 °C, 57% yield). ^{1}H NMR ($CDCl_3$) δ 9.07 (H3′, 1H, dd, J = 1 and 2 Hz), 8.84 (H6′, 1H, dd, J = 1 and 5 Hz), 8.75 (H6 or H6′′′, 1H, ddd, J = 1, 2 and 5 Hz), 8.72 (H6 or H6′′′, 1H, ddd, J = 1, 2 and 5 Hz), 8.68 (H3 or H3′′′, 1H, dd, J = 1 and 9 Hz), 8.50 (H5′′ and H3 or H3′′′, 2H, m), 8.20 (H5′, 1H, dd, J = 2 and 5 Hz), 8.00 (H3′′ and H4′′, 2H, m), 7.89 (H4 and H4′′, 2H, m), 7.36 (H5 and H5′′, 2H, m). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.38; H, 4.64; N, 18.21.

2,2′:3′,2′′:6′′,2′′′-Quaterpyridine (6-2): To a solution of 2,2′-bipyridine (5.0 g, 32 mmol) in freshly distilled diethyl ether (100 mL) under N_2 at -78 °C was added dropwise a 1.5 M solution of lithium diisopropylamide in hexanes. The mixture was allowed to slowly warm to room temperature and stirred for 3 h. The dark purple mixture was quenched by the addition of water (50 mL) with stirring, and the yellow organic layer was separated, dried, and concentrated to a yellow oil. The oil was redissolved in acetone (50 mL) and oxidized by addition of a solution of $KMnO_4$ in acetone until the purple color persisted. The brown slurry was filtered through a bed of Celite to remove MnO_2 and the filtrate was concentrated to a yellow oil. The oil was purified by chromatography on alumina, initially eluted with CH_2Cl_2 to

remove unreacted 2,2′-bipyridine, then followed by CH_2Cl_2/MeOH (98/2). The result was 1.50 g (4.83 mmol) of slightly yellow oil that crystallized with scratching (126-128.5 °C, 30% yield). ^1H NMR ($CDCl_3$) δ 8.79 (H6′, 1H, dd, J = 2 and 5 Hz), 8.63 (H6′′′, 1H, ddd, J = 1, 2 and 5 Hz), 8.44 (H6, 1H, ddd, J = 1, 2 and 5 Hz), 8.28 (H5′′, 1H, dd, J = 1 and 9 Hz), 8.14 (H4′, 1H, dd, J = 2 and 9 Hz), 7.96 (H3′′′, 1H, dt, J = 1, 1 and 9 Hz), 7.70 (H3 and H4 and H4′′ and H4′′′, 4H, m), 7.48 (H5′, 1H, dd, J = 5 and 9 Hz), 7.27 (H5′′′, 1H, m), 7.35 (H3′′, 1H, dd, J = 1 and 9 Hz), 7.16 (H5, 1H, ddd, J = 2, 5 and 9 Hz). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.34; H, 4.67; N, 18.31.

3,2′:4′,3′′-Terpyridine-1-oxide (7-3): A solution of 4-chloro-2,3′-bipyridine-1′-oxide[132] (5-6) (500 mg, 2.42 mmol), diethyl(3-pyridyl)borane (427 mg, 2.90 mmol), and tetrakis(triphenylphosphine) palladium(0) (140 mg, 0.121 mmol) in degassed THF (30 mL) was stirred at room temperature for 0.25 h under N_2. Potassium carbonate (669 mg, 4.84 mmol) in H_2O (10 mL) was then added and the mixture was heated at reflux for 36 h. Following concentrated to a slurry, 50 mL of MeOH was added. The insoluble K_2CO_3 was removed and the filtrate was concentrated onto Kieselgel (2 g). Column chromatography with 80/20 EtOAc/MeOH gave 390 mg (1.56 mmol) of a white solid (mp > 200 °C, 65% yield). ^1H NMR ($CDCl_3$) δ 9.00 (H2′′, 1H, s), 8.95 (H2, 1H, d, J = 2 Hz), 8.83 (H6′′, 1H, d, J = 5 Hz), 8.75 (H6′, 1H, dd, J = 2 and 5 Hz), 8.31 (H6, 1H, dd, J = 2 and 6

Hz), 8.00 (H4 and H4'', 2H, m), 7.91 (H3', 1H, s), 7.58 (H5', 1H, dd, J = 2 and 5 Hz), 7.50 (H5'', 1H, dd, J = 5 and 9 Hz), 7.44 (H5, 1H, dd, J = 6 and 9 Hz). Anal. Calcd. for $C_{15}H_{11}N_3$. $1/2H_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.42; H, 4.34; N, 16.07.

2-Chloro-3,2':4',3''-terpyridine (7-4): A suspension of 3,2':4',3''-terpyridine-1-oxide (7-3) (350 mg, 1.40 mmol) in acetic anhydride (10 mL) was heated at reflux for 24 h. The mixture was concentrated to a brown oil and dissolved in 30 mL of MeOH which was decolorized with charcoal and then filtered through a bed of Celite. The filtrate was concentrated to a yellow solid and washed with 30 mL of diethyl ether to give 200 mg (0.802 mmol) of a yellow solid which is the pyridone (mp 168-172 °C decomp., 57% yield). ^1H NMR (DMSO-d_6) δ 8.98 (H2'', 1H, d, 2 Hz), 8.95 (H3', 1H, d, J = 1 Hz), 8.70 (H6' and H6'', 2H, m), 8.50 (H4, 1H, dd, J = 2 and 8 Hz), 8.18 (H4'', 1H, dt, J = 2, 2 and 9 Hz), 7.69 (H6, 1H, dd, J = 2 and 6 Hz), 7.59 (H5' and H5'', 2H, m), 6.44 (H5, 1H, dd, J = 6 and 9 Hz).

A suspension of this 3,2': 4',3''-terpyrid-2-one (200 mg, 0.812 mmol) in $POCl_3$ (5 mL) and DMF (1 mL) was heated at reflux for 8 h under N_2. The mixture was concentrated to a brown oil and sodium carbonate/ice/H_2O was added until the aqueous phase was basic to pH paper. The aqueous phase was extracted with 50 mL of EtOAc and the organic phase was dried and concentrated to an oil. Column chromatography with

Kieselgel and 80/20 EtOAc/MeOH gave 75 mg (0.28 mmol, 34% yield) of a yellow solid (mp 147-149 °C). ^{1}H NMR ($CDCl_3$) δ 8.96 (H2'', 1H, dd, J = 1 and 2 Hz), 8.84 (H6', 1H, dd, J = 1 and 6 Hz), 8.73 (H6'', 1H, dd, J = 2 and 5 Hz), 8.50 (H6, 1H, dd, J = 2 and 5 Hz), 8.07 (H4, 1H, dd, J = 2 and 8 Hz), 8.01 (H3' and H4'', 2H, m), 7.57 (H5', 1H, dd, J = 2 and 6 Hz), 7.48 (H5'', 1H, ddd, J = 1, 5 and 9 Hz), 7.43 (H5, 1H, dd, J = 5 and 8 Hz). Anal. Calcd. for $C_{15}H_{10}N_3Cl$ .1/2 H_2O: C, 65.10; H, 4.01; N, 15.19: Found: C, 65.40; H, 3.73; N, 15.18.

2,2':3',2'':4'',3'''-Quaterpyridine (7-5): A solution of 2-chloro-3,2': 4',3''-terpyridine (7-4) (70 mg, 0.26 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.013 mmol) in degassed toluene (20 mL) was stirred at reflux for 15 min under N_2. 2-(Tributylstannyl)pyridine[79] (100 mg , 0.261 mmol) was added in three equal portions over 1 hours. The reaction was stirred at reflux for 48 hours and then concentrated to an oil. Column chromatography with alumina and 80/20 EtOAc/hexanes gave 45 mg (0.15 mmol, 58% yield) of a clear oil. ^{1}H NMR ($CDCl_3$) δ 8.80 (H6', 1H, dd, J = 2 and 5 Hz), 8.70 (H6'', 1H, d, J = 6 Hz), 8.63 (H6''', 1H, dd, J = 1 and 5 Hz), 8.58 (H2''', 1H, d, J = 2 Hz), 8.49 (H6, 1H, dt, J = 1, 2 and 6 Hz), 8.14 (H4', 1H, dd, J = 2 and 9 Hz), 7.77-7.65 (H3, H4 and H4''', 3H, m), 7.50 (H5', 1H, dd, J = 5 and 9 Hz), 7.39 (H5'', 1H, dd, J = 2 and 6 Hz), 7.35 (H5''', 1H, dd, J = 5 and 9 Hz), 7.27-7.22 (H3'' and H5, 2H, m). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N,18.05. Found: C, 77.12; H, 4.56; N, 18.03.

3-Chloro-2,4′-bipyridine-1′-oxide (7-6): A degassed toluene (5 mL) solution of 2,3-dichloropyridine (165 mg, 1.12 mmol) and tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.056 mmol) was heated at reflux under N_2 for 1 h. A toluene (30 mL) solution of 4-(tributylstannyl)pyridine N-oxide[113] (860 mg, 2.24 mmol) was added in 1 mL portions over the next 5 h. The mixture was stirred at reflux for 24 h and then cooled to room temperature. The mixture was filtered through a bed of Celite to remove catalyst and the filtrate was concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 160 mg (0.774 mmol) of a slightly yellow solid (mp 135-139 °C, 69% yield). ^{1}H NMR ($CDCl_3$) δ 8.62 (H6, 1H, dd, J = 2 and 6 Hz), 8.28 (H3′, 2H, d, J = 7 Hz), 7.84 (H2′ and H4, 3H, m), 7.31 (H5, 1H, dd, J = 6 and 8 Hz). Anal. Calcd. for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found: C, 55.77; H, 3.68; N, 13.35.

2′,3-Dichloro-2,4′-bipyridine (7-7): A suspension of 3-chloro-2,4′-bipyridine-1-oxide (7-6) (210 mg, 1.02 mmol) in acetic anhydride (10 mL) was heated at reflux for 6 h. The mixture was concentrated to an oil and dissolved in 10 mL of MeOH which was decolorized with charcoal, filtered through a bed of Celite, and concentrated to give 170 mg (0.832 mmol, 81% yield) of a slightly yellow oil. The material was dissolved in $POCl_3$ (5 mL) and DMF (1 mL) and heated at reflux for 24 h. Following concentration, Na_2CO_3/ice/H_2O was added until the aqueous phase was slightly basic to pH paper. The

aqueous phase was extracted with 50 mL of EtOAc and the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel and 100% EtOAc gave 40 mg (0.18 mmol, 22% yield, mp 162-167 °C) of a yellow solid . ^{1}H NMR ($CDCl_3$) δ 8.63 (H6′, 1H, dd, J = 2 and 5 Hz), 8.50 (H6′′, 1H, dd, J = 1 and 6 Hz), 7.85 (H4′, 1H, dd, J = 2 and 9 Hz), 7.73 (H3′′, 1H, dd, J = 1 and 2 Hz), 7.62 (H5′′, 1H, dd, J = 2 and 5 Hz), 7.33 (H5′, 1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45. Found: C, 53.55; H, 2.60; N, 12.44.

3,3′:2′,4′′:2′′,3′′′-Quaterpyridine (7-8): A degassed THF (10 mL) solution of 2′,3-dichloro-2,4′-bipyridine (7-7) (40 mg, 0.18 mmol), diethyl(3-pyridyl)borane (65 mg, 0.44 mmol), and tetrakis(triphenylphosphine) palladium(0) (21 mg, 0.018 mmol) was stirred at room temperature under N_2 for 15 min. Sodium bicarbonate (60 mg, 0.71 mmol) in degassed H_2O (5 mL) was added and the mixture was heated at reflux for 48 h. After cooling to room temperature and dilution with 30 mL of EtOAc, the organic phase was dried and concentrated to an oil. Column chromatography with Kieselgel and 80/20 EtOAc/MeOH gave 25 mg (0.081 mmol, 44% yield) of an oil. ^{1}H NMR ($CDCl_3$) δ ^{1}H NMR ($CDCl_3$) δ 9.00 (H2′′′, 1H, d, J = 2 Hz), 8.83 (H6′, 1H, dd, J = 2 and 5 Hz), 8.68-8.56 (H6′′, H6′′′, H2 and H6, 4H, m), 8.18 (H4′′′, 1H, dt, J = 2, 2 and 9 Hz), 7.87-7.77 (H4′ and H4, 2H, m), 7.56 (H3′′, 1H, dd, J = 1 and 2 Hz), 7.50 (H5′, dd, J = 5 and 9 Hz), 7.37 (H5′′′, 1H, ddd, J = 2, 5 and 9 Hz), 7.29 (H5,

1H, ddd, J = 2, 5 and 9 Hz), 7.14 (H5'', 1H, dd, J = 2 and 6 Hz). Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.10; H, 4.56; N, 18.05.

REFERENCE LIST

(1) Heck, R. F. *Palladium Reagents in Organic Synthesis;* Academic Press: New York, 1985.

(2) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(3) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.

(4) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

(5) Fauvarque, J. F.; Pfluger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419.

(6) Ugo, R.; Pasini, A.; Fusi, A.; Cenini, S. *J. Am. Chem. Soc.* **1972**, *94*, 7364.

(7) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(8) Amatore, C.; Pfluger, F. *Organometallics* **1990**, *9*, 2276.

(9) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655.

(10) Fauvarque, J.F.; Pluger, F.; Troupel, M. *J. Organomet. Chem.* **1971**, *28*, 287.

(11) Fahay, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 2501.

(12) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287.

(13) Isobe, K.; Kawaguchi, S. *Heterocycles* **1981**, *16*, 1603.

(14) Benneche, T. *Acta Chem. Scand.* **1990**, *44*, 927.

(15) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003.

(16) Stille, J. K. *The Chemistry of the Metal-Carbon Bond;* John Wiley: New York, 1985.

(17) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry;* University Science Books: Mill Valley, CA, 1987.

(18) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

(19) Cetinkaya, B.; Lappert, M. F.; McMeeking, J.; Palmer, D.E. *J. Chem. Soc., Dalton Trans.* **1973**, *109*, 1202.

(20) Eaborn, C.; Odell, K.; Pidcock, A. *J. Organomet. Chem.* **1975**, *96*, C38.

(21) Cardin, C. J.; Cardin, D. J.; Lappert, M. F. *J. Chem. Soc., Dalton Trans.* **1977**, 767.

(22) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Organomet. Chem.* **1978**, *146*, 17.

(23) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1978**, 357.

(24) Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1979**, 758.

(25) Atwood, J. D. *Inorganic and Organometallic Reaction Mechanisms;* Brooks-Cole: Monterey, CA, 1985.

(26) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1.

(27) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.

(28) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C. J.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(29) Roth, G. P.; Farina, V.; Liebeskind, L. S.; Penacabrera, E. *Tetrahedron Lett.* **1995**, *36*, 2191.

(30) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

(31) Ohe, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

(32) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

(33) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

(34) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Theis, J. E. *J. Org. Chem.* **1988**, *53*, 2052.

(35) Wright, S. W.; Hageman, D. L.; McLure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(36) Downard, A. J.; Honey, G. E.; Phillips, L. F.; Steel, P. J. *Inorg. Chem.* **1991**, *30*, 2259.

(37) Honey, G. E.; Steel, P. J. *Acta Crystallogr.* **1991**, *C47*, 2247.

(38) Kauffmann, T.; Otter, R.; Greving, B.; König, J.; Mitschker, A.; Wienhöfer, E. *Chem. Ber.* **1983**, *116*, 479.

(39) Constable, E. C.; Elder, S. M.; Healy, J.; Tocher, D. A. *J. Chem. Soc. Dalton Trans.* **1990**, 1669.

(40) Morgan, R. J.; Baker, A. D. *J. Org. Chem.* **1990**, *55*, 1986.

(41) Kem, W. R.; Scott, K. N.; Duncan, J. H. *Experientia* **1976**, *32*, 684.

(42) Ward, M. D. *J. Chem. Soc. Dalton Trans.* **1993**, 1321.

(43) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(44) Terashima, M.; Ishikura, M. *Adv. Heterocycl. Chem.* **1989**, *46*, 143.

(45) Abramovitch, R. A.; Barton, D. H. R.; Finet, J. P. *Tetrahedron* **1988**, *44*, 3039.

(46) Undheim, K.; Benneche, T. *Heterocycles* **1990**, *30*, 1155.

(47) Malm, J.; Hörnfeldt, A. B.; Gronowitz, S. *Heterocycles* **1993**, *35*, 245.

(48) Ohta, A.; Inoue, A.; Ohtsuka, K.; Watanabe, T. *Heterocycles* **1985**, *23*, 133.

(49) Ohta, A.; Ohta, M.; Watanabe, T. *Heterocycles* **1986**, *24*, 785.

(50) Watanabe, T.; Hayashi, K.; Sakurada, J.; Ohki, M.; Takamatsu, N.; Hirohata, H.; Takeuchi, K.; Yasa, K.; Ohta, A. *Heterocycles* **1989**, *29*, 123.

(51) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scripta* **1984**, *23*, 120.

(52) Illuminati, G. *Adv. Heterocycl. Chem.* **1964**, *3*, 285.

(53) Oae, S.; Furukawa, N. *Adv. Heterocycl. Chem.* **1989**, *48*, 1.

(54) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1.

(55) Zoltewicz, J. A.; Kauffman, G. M. *J. Org. Chem.* **1969**, *34*, 1405.

(56) Moran, D. B.; Morton, G. O.; Albright, J. D. *J. Heterocycl. Chem.* **1986**, *23*, 1071.

(57) Busch, M.; Weber, W.; Darboven, C.; Renner, W.; Hahn, H. J.; Mathauser, G.; Stratz, F.; Zitmann, K.; Engelhardt, H. *J. Prakt. Chem.* **1936**, *146*, 1.

(58) Ishikura, M.; Ohta, T.; Terashima, M. *Chem. Pharm. Bull.* **1985**, *33*, 4755.

(59) Murray, J. G.; Hauser, C. R. *J. Org. Chem.* **1954**, *19*, 2008.

(60) Zoltewicz, J. A.; Deady, L. W. *Adv. Heterocycl. Chem.* **1978**, *22*, 71.

(61) Zoltewicz, J. A.; Cross, R. E. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1363.

(62) Shepherd, R. G.; Fedrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.

(63) Bunting, J. W. *Tetrahedron* **1987**, *43*, 4277.

(64) La Costa, W. *Chem. Ber.* **1881**, *14*, 915.

(65) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117.

(66) Bunting, J. W.; Chew, V. S. F.; Sindhuatmadja, S. *Can. J. Chem.* **1981**, *59*, 3195.

(67) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936.

(68) Zoltewicz, J. A.; Kauffman, G. M. *Tetrahedron Lett.* **1967**,337.

(69) Zoltewicz, J. A.; Cruskie, M. P.,Jr.; Dill, C. D. *J. Org. Chem.* **1995**, *50*, 264.

(70) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

(71) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221.

(72) O'Leary, M. H.; Stach, R. W. *J. Org. Chem.* **1972**, *37*, 1491.

(73) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405.

(74) Ishikura, M.; Kamada, M.; Oda, I.; Ohta, T.; Terashima, M. *J. Heterocycl. Chem.* **1987**, *24*, 377.

(75) Terashima, M.; Kakimi, H.; Ishikura, M.; Kamata, K. *Chem. Pharm. Bull.* **1983**, *31*, 4573.

(76) Sugihara, Y.; Miyatake, R.; Takakura, K.; Yano, S. *J. Chem Soc. Chem Commun.* **1994**, 1925.

(77) Mohler, L. K.; Czarnik, A. W. *J. Am. Chem. Soc.* **1993**, *115*, 2998.

(78) Mitchell, T. N. *Synthesis* **1992**, 803.

(79) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731.

(80) Sandosham, J.; Undheim, K. *Tetrahedron* **1994**, *50*, 275.

(81) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993.

(82) Malm, J.; Björk, P.; Gronowitz, S.; Hörnfeldt, A. B. *Tetrahedron Lett.* **1992**, *33*, 2199.

(83) Gundersen, L. L. *Tetrahedron Lett.* **1994**, *35*, 3155.

(84) Undheim, K.; Benneche, T. *Acta Chem. Scand.* **1993**, *47*, 102.

(85) Mitchell, T. N. *Organ. Magn. Reson.* **1975**, 7, 610.

(86) Gundersen, L. L.; Bakkestuen, A. K.; Aasen, A. J.; Overås, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743.

(87) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 200.

(88) Phillips, J. E.; Herber, R. H. *J. Organometal. Chem.* **1984**, *268*, 39.

(89) Weiner, M. A. *J. Organometal. Chem.* **1970**, *23*, C20.

(90) M and T Chemicals Inc. **1979**, (Abstract).

(91) Anderson, D. G.; Webster, D. E. *J. Chem. Soc., Perkin Trans. 1* **1968**, 765.

(92) Zoltewicz, J. A.; Kauffman, G. M.; Smith, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 5939.

(93) Zoltewicz, J. A.; Smith, C. L. *J. Am. Chem. Soc.* **1967**, *89*, 3358.

(94) Van der Stoel, R. E.; Van der Plas, H. C. *J. Chem. Soc., Perkin Trans.* ***1979***, *1*, 2393.

(95) Grigg, R. *J. Heterocycl. Chem.* **1994**, *31*, 631.

(96) Kauffman, G. B.; Pinnell, R. P. *Inorganic Synthesis* **1960**, 6, 3.

(97) Yamamoto, Y.; Azuma, Y.; Mitoh, H. *Synthesis* **1986**, 564.

(98) Friesen, R. W.; Loo, R. W.; Sturino, C. F. *Can. J. Chem.* **1994**, *72*, 1262.

(99) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides;* Academic Press: New York, 1971.

(100) Grimmett, M. R.; Keene, B. R. T. *Adv. Heterocycl. Chem.* **1988**, *43*, 127.

(101) Fife, W. K.; Scriven, E. F. V. *Heterocycles* **1984**, *22*, 2375.

(102) Katritzky, A. R.; Lam, J. N. *Heterocycles* **1992**, *33*, 1011.

(103) Weber, H. *Adv. Heterocycl. Chem.* **1987**, *41*, 275.

(104) Zoltewicz, J. A.; Bloom, L. B.; Kem, W. R. *J. Org. Chem.* **1992**, *57*, 2392.

(105) O'Neil, I. A. *Synlett.* **1991**, 661.

(106) Katritzky, A. R.; Rubio, O.; Szajda, M.; Nowak-Wydra, B. *J. Chem. Res. (S)* **1984**, 234.

(107) Bunting, J. W.; Moors, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 2258.

(108) Heo, C. K. M.; Bunting, J. W. *J. Org. Chem.* **1992**, *57*, 3570.

(109) Ocana, B.; Espada, M.; Avendano, C. *Tetrahedron* **1994**, *50*, 9505.

(110) Kireev, G. V.; Leont'ev, V. B.; Kurbatov, Y. V.; Otroshchenko, O. S.; Sadykov, A. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, *5*, 1034.

(111) Zoltewicz, J. A.; Cruskie, M. P.,Jr. *Tetrahedron* **1995**, *51*, 3103.

(112) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(113) Zoltewicz, J. A.; Cruskie, M. P.,Jr. *J. Org. Chem.* **1995**, *50*, 3487.

(114) Effenberger, F.; Krebs, A.; Williett, P. *Chem. Ber.* **1992**, *125*, 1131.

(115) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.

(116) Rocca, P.; Cochennec, C.; Marsais, F.; Thomasditdumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832.

(117) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 189.

(118) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292.

(119) Yoshino, A.; Nakamura, N.; Takahashi, K. *Bull. Chem. Soc., Jpn.* **1993**, *66*, 1028.

(120) Van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323.

(121) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243.

(122) Levin, J. I. *Tetrahedron Lett.* **1994**, *34*, 6211.

(123) Constable, E. C.; Elder, S. M.; Walker, J. V.; Wood, P. D.; Tocher, D. A. *J. Chem Soc. Chem Commun.* **1992**, 229.

(124) Potts, K. T.; Raiford, K. A. G.; Keshavarzk, M. *J. Am. Chem. Soc.* **1993**, *115*, 2793.

(125) Clew, C. J. B.; Lonsdale, K. *Proc. Roy. Soc. London, Series A* **1937**, *161*, 493.

(126) Osborne, A. G.; Green, R.; Sadler, I. H.; Reed, D. *Magn. Reson. Chem.* **1989**, *27*, 4.

(127) Chaudhuri, P.; Sigel, H. *J. Am. Chem. Soc.* **1977**, *99*, 3142.

(128) Newkome, G. R.; Roper, J. M.; Robinson, J. M. *J. Org. Chem.* **1980**, *45*, 4380.

(129) Cruskie, M. P.,Jr.; Zoltewicz, J. A.; Abboud, K. *J. Org. Chem.* **1995**, in press

(130) Newkome, G. R.; Hager, D. C. *J. Org. Chem.* **1982**, *47*, 599.

(131) Hayes, M. A.; Meckel, C.; Schatz, E.; Ward, M. D. *J. Chem. Soc. Dalton Trans.* **1992**, 703.

(132) Ward, M.D. *J. Chem. Soc., Dalton Trans.*, **1994**, 3095-3098.

(133) Zoltewicz, J. A.; Cruskie, M. P.,Jr. *Tetrahedron* **1995**, in press.

(134) Spotswood, T. M. *Aust. J. Chem.* **1967**, *20*, 1227.

(135) Zoltewicz, J. A.; Helmick, L. S.; O'Halloran, J. K. *J. Org. Chem.* **1976**, *41*, 1303.

(136) Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1982**, *23*, 5291.

(137) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 157.

(138) Constable, E. C.; Seddon, K. R. *J. Chem Soc. Chem Commun*. **1982**, 34.

(139) Constable, E. C. *Tetrahedron* **1992**, *48*, 10013.

(140) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.

(141) Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, *62*, 305.

(142) Baxter, P.; Lehn, J. M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 69.

(143) Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471.

(144) Lukes, R.; Pliml, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1356.

BIOGRAPHICAL SKETCH

Michael P. Cruskie Jr. was born on July 26, 1968, in Troy, New York. He grew up in Schenectady, New York, and attended Niskayuna High School, graduating in June of 1986. While in high school he participated in football, baseball and basketball earning varsity letters his junior and senior year.

In the fall of 1986 he enrolled at St. Lawrence University, where he was a three-year letterman in football. He was also a member of Pi Mu Epsilon (mathematics honors society) and Beta Theta Pi Fraternity. In the summer of his junior year he did an internship as a chemist with General Electric Co. working under Dr. Otto Phanstiel, a graduate of the University of Florida. He received the degree of Bachelor of Science in chemistry and mathematics in May of 1990.

In June of 1990 he moved to Connecticut and began working for Pfizer, Inc., as a laboratory chemist in their medicinal research department.

In January of 1992 he enrolled at the University of Florida to pursue the degree of Doctor of Philosophy in organic chemistry. After completion of his degree, he will be moving to Indianapolis, Indiana, to work for Reilly Industries Inc., a pyridine chemical company.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John A. Zoltewicz, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier Jr
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth Wagener
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

James M. Boncella
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Koppaka V. Rao

Koppaka V. Rao
Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1995

Dean, Graduate School